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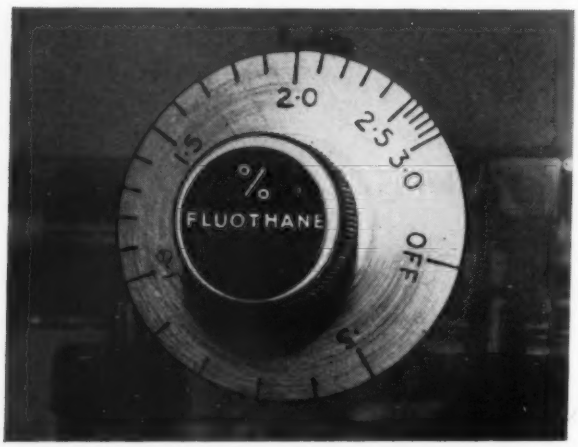

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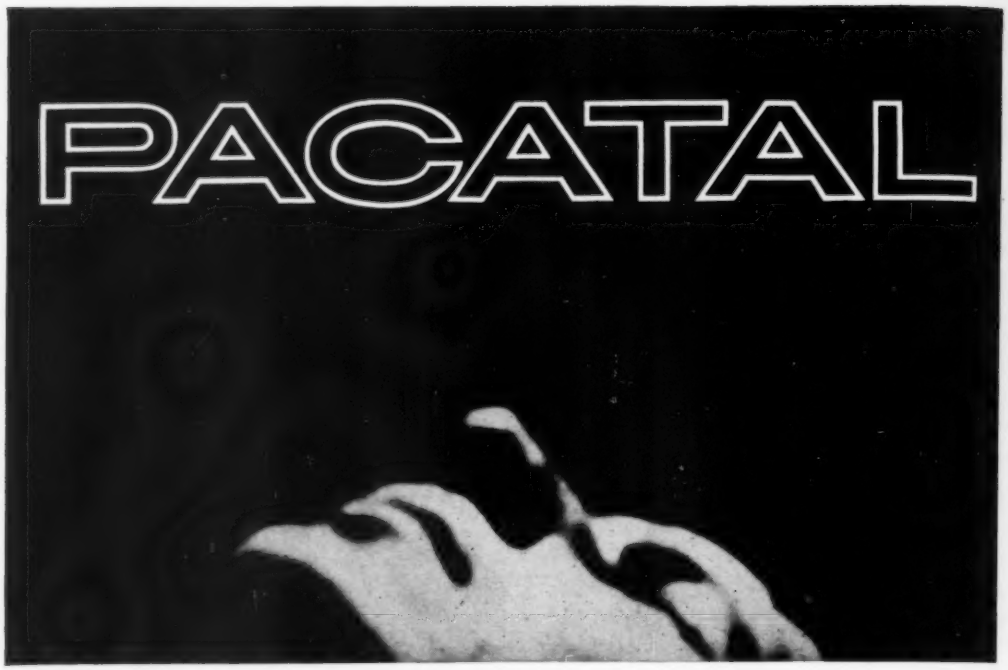

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXIX No. 7 JULY 1957

EDITORIAL

SENIOR HOSPITAL MEDICAL OFFICERS IN ANAESTHESIA

MAYBE the setting up of a Royal Commission by H.M. Government to examine the terms of service of doctors in the National Health Service was a move open to criticism. But wisdom dictates that this important body should be given all the help possible in this really very difficult task. The problems of anaesthetists cannot be regarded in any different light from those of other consultants except in one particular. It was decided on the formulation of the National Health Service that anaesthesia should be one of those specialties in which there was a place for the Senior Hospital Medical Officer—a non-consultant, non-trainee, specialist grade. Those bodies, both academic and political, which can speak with authority on subjects concerned with anaesthesia and the anaesthetic service to patients have unanimously and consistently deplored this decision. Their wisdom in so doing has not been brought into question by any new factor since 1948. This reaction was based on two objections: (1) anaesthesia was thus differentiated from other branches of medicine with no greater clinical responsibilities; (2) the grade was not intrinsically a stepping stone to consultant status.

Those who are in this grade of Senior Hospital Medical Officer and who devote their whole time to their specialty, be it anaesthesia or any other, find themselves in a frustrating position with apparently little future. They are too busy to work for higher qualifications and, as they have reasonable remuneration, they often lack the competitive initiative. They have a wide experience of the technology of this subject, but may feel that in so much as they are not consultants they cannot be expected to give consultant service. Yet the post of Senior Hospital Medical Officer has been so abused that in many instances there would appear little to differentiate the ordinary day-to-day work in such a position from that of many consultants. The B.M.A. is at the moment conducting a survey to ascertain which of these individuals it feels able to recommend for consultant remuneration on the grounds of the service being given and the work being done. But what of the remainder? They could not be recommended as consultants by any responsible tribunal. It would seem that they must be regarded as the casualties of evolution and slowly, like old soldiers, fade away. It is to be hoped that such posts will not be perpetuated, but that the sessions will be divided among other grades.

The giving of an anaesthetic is a highly responsible procedure and entails considerable hazards which only sound clinical judgment can avoid. There is no place here for the mere technician, who must, it seems, be engendered by a subconsultant grade of specialist with no prospects of promotion. Whether or not a junior specialist grade should be established as a step on the ladder to consultant status in all branches of medicine is not the point at issue, and there may be much to be said for it, but again we repeat, the gradual disappearance of the Senior Hospital Medical Officer grade as it exists at present in anaesthesia can do nothing but good. The service to patients will be better and more safely carried out by consultants assisted, in certain localities and under special circumstances, by trainee grades and by General Practitioners who have had special training and hold suitable qualifications and who are moreover prepared to devote a reasonable amount of time to their hospital duties.

Brit. J. Anaesth. (1957), **29**, 294

RELEASE OF ADRENERGIC CATECHOLS AFTER THE ADMINISTRATION OF HEXAMETHONIUM BROMIDE

BY

L. W. HALL

Department of Veterinary Clinical Studies, University of Cambridge

THE use of hexamethonium to produce controlled hypotension has been the subject of many reports and a number of these have noted that often satisfactory ischaemia was not obtained at the operation site (Enderby, 1950, 1951a, 1951b, 1952; Pelmore and Enderby, 1951; Boyan and Brunschwig, 1952). Coulter (1957) considers that this failure was probably due to the presence of circulating adrenaline, and perhaps noradrenaline, causing a direct vasoconstriction and tachycardia thus increasing the blood pressure.

The chromaffin secretory cells of the adrenal medulla are richly innervated (Willard, 1936) by preganglionic fibres (Elliott, 1913), and are derived from the neural crest of the embryo; thus they are thought to be homologous with the sympathetic ganglionic cells. Acetylcholine is released in the adrenal medulla when the splanchnic nerve is stimulated and this compound appears to cause the secretion of adrenaline (Feldberg, Minz and Tsudzimura, 1934). The junction between the preganglionic nerve fibre and the secretory cell may, therefore, be regarded as a ganglionic synapse (Herman, 1939, 1942). It has been shown, moreover, that ganglionic synapses vary in their sensitivity to hexamethonium (Paton and Zaimis, 1952) and it is possible that the doses of hexamethonium used in the apparently resistant cases were not capable of blocking transmission at the junction between the preganglionic fibres and the chromaffin cells, although they were sufficient to prevent transmission in most peripheral autonomic ganglia.

If the junctions between the preganglionic fibres and the chromaffin secretory cells were not blocked by hexamethonium, a fall in the blood pressure could result in a reflex release of adrenaline and noradrenaline from the adrenal glands. Since the normal blood pressure regulating mechanisms would be blocked by hexamethonium, it is probable that the presence of very small quantities of these adrenergic catechols in the circulating blood would have a marked effect. Because the quantitative measurement of very small blood levels of these substances is difficult it was decided to carry out experimental studies in dogs and cats in an attempt to produce indirect evidence of their reflex release from the adrenal glands after the administration of hexamethonium.

The main objects of this experimental study were to discover whether hypotension induced by hexamethonium might cause the release of adrenergic catechols from the adrenal glands, and if so, whether this was a reflex effect involving the cardio-aortic, carotid sinus and splanchnic nerves respectively.

METHODS

Dogs were anaesthetized by the premedication – thiopentone – nitrous oxide/oxygen/trichloroethylene sequence or by intermittent intravenous injections of thiopentone sodium, or by chloralose (0.09–0.1 g/kg body weight, intravenously) after induction with intravenous thiopentone sodium. Cats were anaesthetized with pentobarbitone sodium (0.03 g/kg body weight, intravenously) or chloralose (0.08 g/kg body weight, intravenously) after induction with ether.

In cats the adrenal glands and splanchnic nerves were exposed by the extraperitoneal route through an incision parallel to, and about one centimetre below, the transverse processes of the lumbar vertebrae. In dogs the exposure was made by resection of the last rib.

In experiments where the vagus nerves were sectioned they were cut in the neck at the level of the cricoid cartilage of the larynx.

Bilateral denervation of the carotid sinuses was performed by careful and thorough stripping of the adventitia from the wall of the arteries in the region of the sinus.

Two dogs were prepared for subsequent experiment by section of their splanchnic nerves by previous aseptic operation. The splanchnic nerve was pulled through the diaphragm from the abdomen into the thorax and divided close to the diaphragm. The sympathetic chain was then dissected away, cutting the rami communicantes up to the eleventh thoracic segment, and excised at this level. The excision was carried out on the other side of the animal 10 days after the first operation and the dogs were not used for experiment until 14 days after the second operation.

Intra-arterial injections of acetylcholine were given through a radio-opaque catheter introduced into the aorta, from a branch of the femoral artery, under radiographic control. The catheter tip was positioned in the aorta immediately above the origin of the right renal artery, and its exact positioning was confirmed later at autopsy. The aorta was occluded just below the origin of the left renal artery as the injection was made.

The systemic blood pressure was recorded on a mercury manometer connected to either the carotid, brachial or femoral arteries. The respiratory rate was recorded by a stethograph/tambour system. Nerves were stimulated by means of an induction coil (Baird and Tatlock, London, Ltd.), the primary coil of which was connected to a 2-volt accumulator battery.

The drugs and their solutions used were:

(1) Thiopentone sodium ("Intraval Sodium," May and Baker Ltd.): 5 per cent aqueous solution.

(2) Chloralose (British Drug Houses Ltd.): 1 per cent aqueous solution.

(3) Pentobarbitone sodium (Abbott Laboratories Ltd.): solution containing 65 mg/ml.

(4) Hexamethonium bromide ("Vegolysen," May and Baker Ltd.): 1 per cent w/v solution.

(5) 2-(N-p-tolyl-N-m hydroxyphenyl-aminomethyl-imidazoline methanesulphonate ("Rogitine," Ciba Laboratories Ltd.): solution containing 5 mg/ml.

(6) 2-(l-piperidylmethyl)-1, 4 benzodioxan ("Piperoxane," May and Baker Ltd.): solution containing 2 mg/ml.

(7) Atropine sulphate (British Drug Houses Ltd.): weighed quantities dissolved in 0.9 per cent NaCl immediately before injection.

(8) Acetylcholine (Roche Products Ltd.): a stock solution containing 2 mg/ml in 5 per cent sodium dihydrogen phosphate solution, stored in the frozen state.

(9) Adrenaline hydrochloride 1:1,000 w/v solution (May & Baker Ltd.), diluted to 10 μg of base per millilitre with 0.9 per cent NaCl immediately before use.

RESULTS

(a) *Characteristic reaction to hexamethonium bromide.*

Hexamethonium bromide was administered intravenously to 11 dogs and 4 cats to study the effects produced by a dose of 2 mg/kg.

After the injection of the drug there was an initial sharp fall in the blood pressure, followed by a rise which was succeeded by a secondary fall. Finally there was a slow recovery to almost the pre-injection level. (This response has been divided into four phases by Szutu and Schweitzer (1954). The phase I of these authors corresponds to the initial fall, phase II to the rise, and phase III to the secondary fall in the blood pressure, respectively. They designated the slow recovery period as phase IV.) Changes in the respiratory rate also occurred; there was a temporary increase in the rate coinciding with the initial fall and succeeding rise of the blood pressure (fig. 1).

To demonstrate the effect of hexamethonium on ganglionic transmission, the left vagus nerve was cut in four dogs and its peripheral end stimulated with stimuli of 5 seconds duration. After the administration of 2 mg/kg of hexamethonium bromide it appeared that only the first few impulses in the nerve were transmitted to the myocardium (fig. 2).

(b) *Differential blocking action of hexamethonium bromide.*

Stimulation of the peripheral end of the cut left splanchnic nerve in dogs as well as in cats produced a rise in blood pressure which occurred

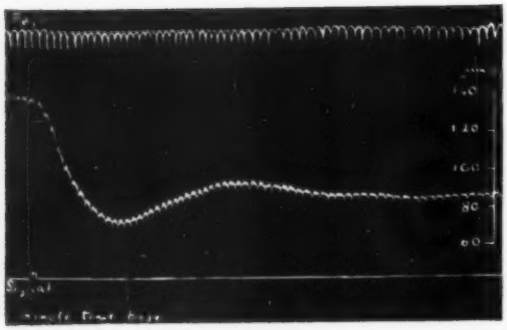
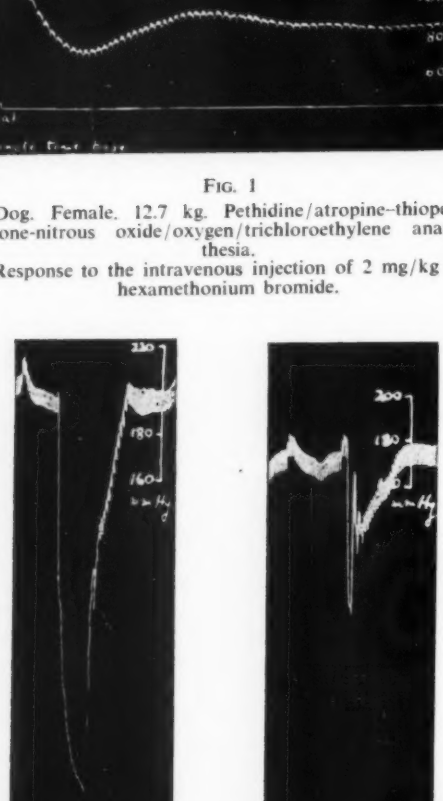


FIG. 1

Dog. Female. 12.7 kg. Pethidine/atropine–thiopentone-nitrous oxide/oxygen/trichloroethylene anaesthesia.
Response to the intravenous injection of 2 mg/kg of hexamethonium bromide.



(*a*) (*b*)

FIG. 2

Dog. Female. 12.3 kg. Thiopentone anaesthesia.
(*a*) Stimulation of the peripheral end of cut left vagus nerve.
(*b*) Stimulation of the peripheral end of cut left vagus nerve after the injection of 2 mg/kg of hexamethonium bromide.

in two stages. The first stage was due to vasoconstriction in the splanchnic vascular bed, while the second was due to the release of adrenergic catechols from the adrenal medulla (von Anrep, 1912). After removal of the adrenal gland, the rise in blood pressure which resulted from stimulation of the nerve, i.e., the vasoconstrictor response, was completely abolished by the injection of 2 mg/kg of hexamethonium bromide.

Before the removal of the adrenal gland stimulation of the peripheral end of the divided left splanchnic nerve trunk caused a rise in the blood pressure, even after the administration of this same dose of hexamethonium bromide. This rise in the blood pressure did not commence immediately the nerve was stimulated but it persisted for some time after the stimulation ceased. In these circumstances this rise could only have been due to the release of adrenergic catechols from the adrenal medulla. That this was indeed the case was indicated by the fact that this response was abolished by the intravenous injection of 1 mg/kg of 2-(l-piperidylmethyl)-1, 4 benzodioxan (Piperoxane), an adrenergic blocking agent, after the hexamethonium and prior to stimulation of the nerve.

Thus under these experimental conditions a dose of 2 mg/kg of hexamethonium bromide was shown to block transmission to the postganglionic vasomotor nerves but it did not prevent the release of adrenaline from the adrenal medulla. An increase in the dose of hexamethonium to 6 mg/kg usually, but not invariably, prevented this release of adrenaline.

The relative resistance of the synaptic transmission in the adrenal medulla to hexamethonium blockade was also demonstrated by a further experiment. In cats, stimulation of the peripheral end of the divided left splanchnic nerve with stimuli of 5 seconds duration, given at 5-minute intervals, could be carried out for over 3 hours with no sign of fatigue. After 6 mg/kg of hexamethonium bromide similar stimulation caused the release of adrenaline from the adrenal medulla about 30 to 40 minutes after the administration of the hexamethonium, but the vasoconstrictor response was not apparent until 50 to 70 minutes from the time of injection.

These results were all obtained irrespective of the nature of the anaesthetic used in the experiment, but the rise in the blood pressure following the release of adrenaline was greater in animals under chloralose anaesthesia. This was in accordance with the finding of Vincent and Thompson (1928) that chloralose potentiates the effects of splanchnic nerve stimulation.

(c) *The action of hexamethonium bromide after removal of the adrenal glands.*

The intravenous injection of 2 mg/kg of hexamethonium bromide after removal of the adrenal glands produced a profound fall in the blood pressure which then very slowly returned to the pre-injection level. The second and third phases of the blood pressure response obtained in normal animals were usually absent; when they occurred they were of very small magnitude. The respiratory frequency increased as the blood pressure fell, the original rate being resumed about 2 minutes after the injection of the drug.

It was considered that any rise in blood pressure corresponding to the second phase of the normal response could be accounted for by an increase in the cardiac output from a temporarily augmented venous return due to the increase in the respiratory rate.

(d) *The action of hexamethonium bromide when given after the administration of an adrenolytic drug.*

In dogs under thiopentone anaesthesia it was found that the usual pressor response to the intravenous injection of 0.25 μg/kg of adrenaline was abolished or converted into a fall in blood pressure if 1 mg/kg of 2-(N-p-tolyl-N-m hydroxyphenyl-aminomethyl)-imidazoline methanesulphonate (Rogitine) was given by intravenous injection 3 minutes before the injection of the adrenaline. After this dose of Rogitine stimulation of the peripheral end of the divided left vagus still slowed the heart and thus this dose probably produced little or no blockade of the autonomic ganglia.

Doses of 2 mg/kg of hexamethonium bromide given to dogs which had received 1 mg/kg of Rogitine produced a response similar to that seen after removal of the adrenal glands.

(e) *Experiments designed to delay the release of adrenaline into the circulation after the injection of hexamethonium bromide.*

The foregoing results showed that after the intravenous injection of 2 mg/kg of hexamethonium bromide there was, in normal animals, a tendency for the blood pressure to be at least partially restored after the initial fall by the operation of two separate mechanisms. First, there was the temporary increase in the respiratory rate which occurred with the initial fall in the blood pressure. This increase was accompanied by a slight rise in the blood pressure which fell again as the respiratory rate returned to normal. Secondly, there was a release of adrenaline from the adrenal medulla due to impulses passing down the preganglionic fibres of the splanchnic nerves. It was believed that this release of adrenaline was the main factor which determined the magnitude of phase II of the blood pressure response. The existence of these separate mechanisms could be further demonstrated by arranging that there should be a delay between the release of adrenaline from the adrenal medulla and its entrance into the general circulation. In two dogs under thiopentone anaesthesia the right adrenal gland was removed and a light rubber-shod clamp placed around the left adrenal gland in such a way as to occlude the gland from the circulation. Hexamethonium bromide (2 mg/kg) was injected intravenously and the clamp removed from vessels of the left adrenal gland about 2 minutes after the injection of the drug.

The blood pressure fell after the injection of the hexamethonium, showed a slight rise as the respiratory rate increased, and fell again as the respiratory rate returned to the original frequency. The release of the clamp from adrenal vessels was followed by a marked and persistent rise in the blood pressure which then returned gradually to near that seen before the injection of the hexamethonium (fig. 3).

These results appeared to confirm the existence of the two separate mechanisms but this interpretation might be criticized on the grounds that the adrenal gland became anoxic while the clamp was in position. The adrenaline liberated into the circulation by the removal of the clamp might, therefore, have been released in the gland in

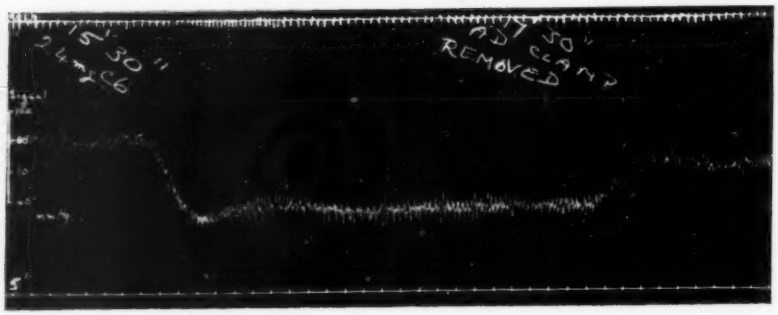


FIG. 3
Dog. Male. 11.8 kg. Thiopentone.
Right adrenal gland removed. Left adrenal blood vessels clamped, hexamethonium given and the clamp removed.

response to this anoxia and not in response to nerve impulses in the splanchnic nerves.

In a further series of experiments anoxia was avoided by delaying the entrance of adrenaline into the circulation by diverting the adrenal vein blood so that it flowed through a length of polythene tubing before returning to the venous system. Thus there was now no interruption of the adrenal circulation.

Under thiopentone anaesthesia the right adrenal gland was removed as in the previous experiment. The left lumbar vein was isolated, all its tributaries tied and the vein itself ligated distally. A 2-mm bore polythene catheter was introduced into the vein so that its tip was at the adrenal hilus. The vein was then ligated between the adrenal gland and the posterior vena cava, causing the venous blood leaving the adrenal gland to flow through the catheter. This adrenal effluent was led to a siliconed glass drip chamber and thence through more polythene tubing to be returned to the circulation via the right femoral vein. It was found that there was an optimum length for the polythene tube and best results were obtained when the extracorporeal circulation had a capacity of about 6 ml. At this stage the animal was given an intravenous injection of 5 mg/kg of heparin (British Drug Houses Ltd.). Hexamethonium bromide (2 mg/kg) was then injected intravenously and the behaviour of the blood pressure observed.

In two dogs the blood pressure response to the injection of hexamethonium was similar to that seen in normal intact animals but there was an additional rise in the blood pressure occurring about 4 minutes after the injection of the drug and forming a distinct "step" in the fourth phase of the response (fig. 4). The blood flow through the adrenal vein catheter was approximately 2 ml/min and thus blood leaving the adrenal gland would not enter the general circulation until about 3 minutes after it had passed from the gland. There would therefore be a delay of this same time between the release of adrenaline from the adrenal medulla and its appearance in the systemic circulation. In these circumstances the occurrence of the "step" in the fourth phase of the response could well have been due to the operation of the second of the proposed compensatory mechanisms.

The marked rise in the blood pressure during the second phase of the response indicated that it was possible for some blood to leave the adrenal medulla and enter the general circulation without having to pass through the polythene catheter. Attempts to isolate the gland more completely were unsuccessful due to denervation.

(f) *The action of hexamethonium bromide in dogs after division of their splanchnic nerves.*

In the two dogs which had undergone section of their splanchnic nerves at a previous operation the intravenous injection of 2 mg/kg of hexamethonium bromide produced a response similar to that seen in animals in which the adrenal glands had been removed. The second and third phases of the blood pressure response shown by normal

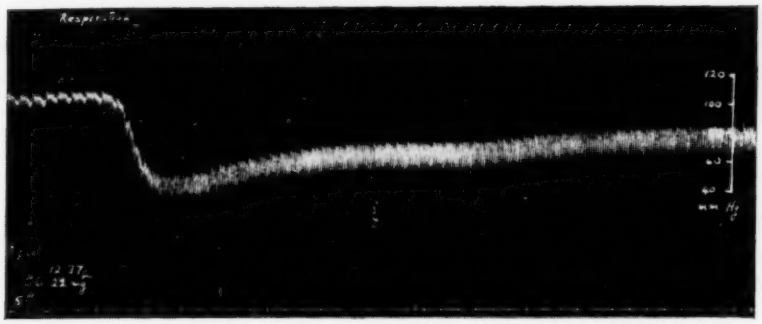


FIG. 4

Dog. Male. 11 kg. Thiopentone.
Right adrenal gland removed. Left adrenal venous effluent diverted to right femoral vein. Effect of intravenous injection of 2 mg/kg hexamethonium bromide.

animals were absent in one dog and of very small magnitude in the other. In this second dog the occurrence of phase II and phase III of the response could be accounted for by the observed temporary increase in the respiratory frequency.

In order to prove that in these dogs the adrenal glands were still capable of releasing adrenaline into the circulation the following procedure was carried out. The vagus nerves were divided and 1 mg/kg of atropine sulphate was injected intravenously. Five minutes later acetylcholine was injected into the aorta immediately above the origin of the right renal artery. The aorta was occluded just posterior to the origin of the left renal artery while the injection was made, the effects of such occlusion having previously been noted for control purposes. The injection of acetylcholine was followed by a rise in the blood pressure, thus demonstrating that the release of adrenaline from the adrenal glands could occur in these dogs.

(g) *The effect of hexamethonium bromide given after section of the vagus nerves.*

Section of the vagus nerves before the injection of 2 mg/kg of hexamethonium bromide modified the blood pressure response to this drug. In the first three dogs in which the experiment was performed the secondary rise which normally follows the initial fall in the blood pressure was absent. In a fourth dog the initial fall was followed by a sharp rise of about 20 mm of mercury, after which the blood pressure made a gradual recovery to the pre-injection level. In none of the dogs was the fall in the blood pressure accompanied by any change in the respiratory rate.

(h) *The effects of hexamethonium bromide when given after section of the vagus nerves and denervation of the carotid sinuses.*

After section of the vagus nerves and denervation of the carotid sinuses the intravenous injection of 2 mg/kg of hexamethonium bromide caused a fall in the blood pressure which was not accompanied by any change in the respiratory rate. There was no evidence of any secondary rise in the blood pressure.

DISCUSSION

These experiments have demonstrated that there are two mechanisms which are responsible for the partial restoration of the blood pressure after it has been reduced as a result of the blockade of the autonomic ganglia by 2 mg/kg of hexamethonium bromide. First, there is the temporary increase in the respiratory rate which coincides with phase I and phase II of the blood pressure response. Secondly there is a reflex release of adrenergic catechols from the adrenal medulla.

The respiratory mechanism was clearly demonstrated since the respiratory rate always increased as the blood pressure fell. Although only of short duration, the increase was invariably accompanied by a rise in the blood pressure, and after removal

of the adrenal glands, or the administration of an adrenolytic drug such as Rogitine, prior to the injection of hexamethonium, this rise in the blood pressure persisted only as long as the increase in the respiratory rate was apparent. The rise in blood pressure is presumably due to a rise in the cardiac output since the increased frequency of respiration should augment the venous return to the heart.

When the respiration had returned to the pre-injection rate the blood pressure was still always higher than the minimum reached during the initial fall. This has been shown to be due to the release of adrenergic catechols from the adrenal medulla.

The experiments in which the release of the catechols was delayed by clamping of the blood vessels to the adrenal gland, separated the effect of the increase in the respiratory rate from that due to the release of these substances (fig. 3). It may, however, be asserted that clamping of the blood vessels, by inducing anoxia in the gland, produced a release of hormones from the medullary cells. This has in fact been suggested by Bülbring, Burn and de Elio (1948), but it is important to note that in their experiments the gland was perfused with blood from a pump-oxygenator and that anoxia was continued for 30 minutes, during which time the adrenaline concentration in the effluent from the gland rose from $1\frac{1}{2}$ to 4 μg/ml. In the experiments reported here conditions were more akin to those of Posternak and Larrabee (1950) who produced ischaemia of the adrenal glands by clamping the posterior aorta and vena cava. These workers considered that the effects they demonstrated could be interpreted as indicating that adrenal hormones were secreted no more rapidly in an ischaemic than in a normal gland, although after a period of circulatory stasis the catechol content of the glands would naturally be higher than in normal glands. Since, in the experiments illustrated in figure 3, the rise in the blood pressure produced on release of the clamps was very similar to that found in intact animals, it can be argued that the liberated pressor amines were not produced in response to local anoxia in the ischaemic gland, but were released reflexly as a result of the rapid fall in the blood pressure.

In an attempt to demonstrate that this was indeed the case, the delivery of the adrenal venous blood into the general circulation was delayed, in a further series of experiments, by leading it through polythene tubing and delivering it to the femoral vein. The results were not so clear cut because there was a primary rise in the blood pressure preceding that due to the adrenergic catechols contained in the blood diverted to the femoral vein. This primary rise in blood pressure occurred both after the administration of hexamethonium and after direct stimulation of the peripheral end of the cut splanchnic nerve. The most reasonable explanation for these results is that the total venous effluent from the adrenal gland was not diverted through the polythene tubing to the femoral vein, but that a subsidiary venous drainage as noted by Flint (1900) was responsible for returning some of the adrenal venous blood directly into the general circulation. Flint used histological methods and showed that a few medullary veins ran outwards to the capsule of the gland where they emptied into a venous plexus which drained into the lumbar, phrenic and renal veins. The results reported here indicate that subsidiary channels may in fact return quite a significant proportion of the adrenal venous blood to the general circulation.

The release of catechols from the adrenal glands during the period of hypotension induced by hexamethonium would appear to depend on a diminution in the afferent discharges which are responsible for inhibition of the centres of the medulla oblongata. Since the effects were abolished by section of the nerves of Hering and the vagus nerves, it can be assumed, with some confidence, that the sensory receptors involved in the response are the baroceptors of the cardio-aortic and carotid sinus areas. It may be that the baroceptors of the cardio-aortic area are the more important receptors since section of the vagus nerves alone usually, but not always, abolished the rise in the blood pressure attributable to the release of adrenal medullary hormones. In all cases, section of both the vagus and carotid sinus nerves completely abolished this effect.

The efferent nerves involved have been shown to be the splanchnic nerves and the posterior

thoracic sympathetic nerve chains since after denervation of the adrenals by section of these nerves (Stewart and Rogoff, 1916) hypotension induced by hexamethonium was not followed by the release of hormones from the medulla.

The resistance of synaptic transmission at the junction between the preganglionic fibres and the chromaffin cells of the adrenal to hexamethonium blockade appeared to be greater than that indicated by the results of other workers. Transmission at this junction is blocked by a dose of 10 mg/kg of tetraethylammonium (Morrison and Farrar, 1949; Malmèjac, Chardon and Neverre, 1951), and hexamethonium has been shown to be about twenty times more potent than this agent in blocking transmission in the superior cervical ganglion of the cat (Paton and Zaimis, 1949). While there is no direct comparison between the action of tetraethylammonium salts and hexamethonium on the synapses of the adrenal medulla, a dose of 6 mg/kg of hexamethonium, which according to these results should represent a considerable dose of tetraethylammonium, did not always prevent the release of adrenal medullary hormones on stimulation of the peripheral end of the cut splanchnic nerve.

The action of hexamethonium on ganglionic transmission appears to be similar to the effect of denervation. About 40 hours after section of the preganglionic fibres, transmission through a ganglion is impaired and the synthesis of acetylcholine in the ganglion is reduced (Brown and Feldberg, 1936a; Feldberg, 1943; Banister and Scrase, 1950). The impairment of transmission appears to be due to the low concentration of acetylcholine available in such a denervated ganglion, only the first few impulses of any preganglionic volley being transmitted to the postganglionic fibres. A similar impairment of transmission was seen when the peripheral end of the cut vagus nerve was stimulated after the injection of 2 mg/kg of hexamethonium bromide (fig. 2). An explanation for this might be found in the changes which occur in the concentration of acetylcholine released in a ganglion during the course of a preganglionic volley. Brown and Feldberg (1936b) showed that a large quantity of acetylcholine was released at the preganglionic fibre terminals from an inactive store at the start of a period of stimulation and that on continued stimulation the amount was lowered until presumably it became equal to that synthesized. Since hexamethonium competes with acetylcholine for the receptor sites (Paton and Zaimis, 1952), in its presence transmission will only occur when the concentration of acetylcholine is high. It may be, therefore, that the brief transmission which was noted was due to the release of the large amount of acetylcholine from the inactive store and that after a short period of stimulation its concentration was too low for it to compete successfully with the hexamethonium.

Clearly if a similar impairment of transmission occurs at the junction between the preganglionic fibres and the chromaffin cells of the adrenal medulla the increased discharge of adrenaline which follows the administration of hexamethonium will soon cease. However, even if this increase is only transient, its effects may be prolonged since hexamethonium potentiates the action of adrenaline by suppressing the normal compensatory mechanisms (Paton and Zaimis, 1952).

SUMMARY

(1) The action of hexamethonium bromide in anaesthetized cats and dogs has been examined to determine whether the difficulty experienced in achieving satisfactory levels of hypotension by the use of this agent in clinical anaesthesia could be due to the action of hormones released reflexly from the adrenal medulla.

(2) The resistance to hexamethonium blockade of the junction between the preganglionic nerve fibres and the chromaffin cells of the adrenal medulla was found to be greater than that of the ganglionic synapses of the splanchnic vasoconstrictor nerves.

(3) It was found that the initial fall in the blood pressure induced by the intravenous injection of 2 mg/kg of hexamethonium bromide resulted in (i) a transitory increase in the respiratory rate, which coincided with a temporary and slight increase in the blood pressure, and (ii) a release of medullary hormones from the adrenal glands. These hormones produced an immediate and sustained rise in the blood pressure.

(4) The release of adrenergic catechols which followed the intravenous injection of 2 mg/kg of hexamethonium bromide would appear to depend on a diminution in the sensory discharge which results in inhibition of the centres of the medulla oblongata. The afferent nerves involved have been shown to be the nerves of Hering and the vagus nerves. It is assumed that the sensory receptors are the baroceptors of the cardio-aortic and carotid sinus areas. The efferent nerves were found to run in the splanchnic nerves and in the posterior thoracic sympathetic nerve chains.

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EXPERIMENTAL STUDIES WITH PRESTONAL, A NEW SHORT-ACTING MUSCLE RELAXANT

BY

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MANY anaesthetists feel that a nondepolarizing relaxant combining brief duration of action with easy reversibility by neostigmine or edrophonium (Tensilon) would be a most useful drug (Foldes, 1956). The first clinical observations (Frey, 1955) suggested that Prestonal (N,N,N^1,N^1,-tetramethyl-N,N^1-bis-(carbopropoxymethyl)-3 14-dioxahexadecane-1, 16-diammonium bromide) might fulfil these requirements.

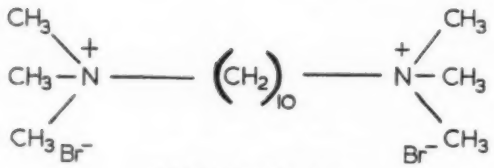
Prestonal (see figure 1) is chemically related to decamethonium. It differs from the latter by the lengthening of the decamethylene chain with two oxyethyl groups and by the substitution of a carbopropoxy group into one of the methyl groups on both quaternary nitrogens. It has been shown previously that both lengthening the distance between the two quaternary nitrogens (Zaimis et al., 1952), and substitution of larger radicals in place of the methyl groups attached to the quaternary nitrogens (Ginzel et al., 1951; Randall, 1952; Hoppe et al., 1953) tend to reduce the depolarizing effect of muscle relaxants. It was anticipated that as a result of these structural changes Prestonal would produce a short and easily reversible nondepolarizing block. Consequently, experiments were designed to obtain information on the potency and duration of action as well as the type of myoneural block produced by Prestonal in man.

MATERIAL AND METHODS

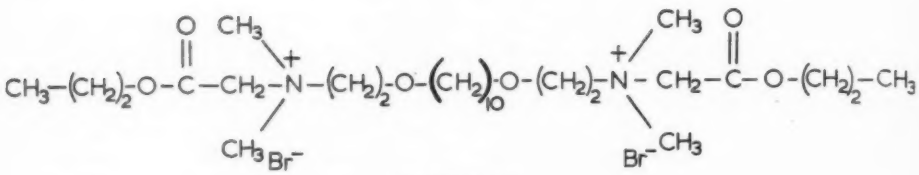
The investigations to be described were carried out on 51 patients undergoing various surgical procedures under spinal analgesia not extending above the level of the tenth dorsal segment. This method of anaesthesia itself has little effect on respiration, and, at the same time, excludes the influence of surgical stimuli on respiration. For the patient's comfort and to eliminate the effects of emotional influences on respiration, light general anaesthesia was maintained throughout. After spraying the patient's mouth and pharynx with 1 per cent amethocaine hydrochloride solution, a sleeping dose of thiopentone was administered and an oral airway inserted. Anaesthesia with nitrous oxide and oxygen was started at a flow rate of 4 litres and 2 litres per minute respectively. The flow rate was reduced to a maintenance level of 500 ml of each gas when most of the patient's nitrogen had been eliminated. Sufficient pethidine (25–50 mg) was then given intravenously to maintain a stable plane of anaesthesia. For the same reason, additional small doses of thiopentone were also given in the course of the experiment as required. When general anaesthesia became stabilized, control values for tidal volume, respiratory rate, pulse rate and blood pressure were obtained. Tidal volumes were measured with a Bennett ventilation meter incorporated into the CO_2 circle absorption system. Whenever necessary for the patient's welfare, assisted or controlled respiration was used. In representative experiments, tidal volume changes were also recorded graphically by connecting a spirometer in place of the breathing bag of the anaesthesia apparatus. The presence or absence of flushing after the administration of Prestonal was also noted.

The drugs used and their doses were:

Prestonal 1.5 or 0.75 mg/kg.
Edrophonium (Tensilon) 0.3 mg/kg.
Pyridostigmine (Mestinon) 0.15 mg/kg.
Neostigmine (Prostigmine) 0.02 mg/kg.



DECAMETHONIUM



PRESTONAL

FIG. 1

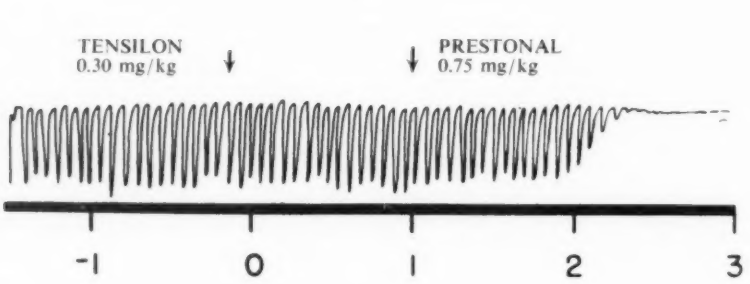


FIG. 2

The influence of edrophonium (Tensilon) on the respiratory effect of Prestonal.
Note that 0.3 mg/kg edrophonium has no effect on tidal volume. The same dose of edrophonium given when tidal volume recovered to 50 per cent of control caused apnoea.

All drugs were injected into the tubing of the intravenous infusion. The doses of Prestonal were injected in 30 seconds; all other drugs were injected as rapidly as feasible through a No. 22 s.w.g. needle. The duration of respiratory depression was defined as the time elapsed between the start of apnoea and the return of the tidal volume to the control value.

Experimental Procedure.

(A) 1.5 mg/kg of Prestonal was administered intravenously to 31 patients. Twenty-six of these received an additional 0.75 mg/kg dose of Prestonal when the tidal volume returned to control value. Twenty-one of the 26 patients were given a second 0.75 mg/kg dose of Prestonal when the tidal volume returned to normal after the first 0.75 mg/kg dose.

(B) Ten patients were given an initial 0.75 mg/kg dose of Prestonal followed 30 minutes later by a second identical dose. Another 10 patients in this group were given 0.3 mg/kg of edrophonium one minute before the initial 0.75 mg/kg dose of Prestonal. In these patients a second identical dose of Prestonal was given 30 minutes later, this time not preceded by edrophonium.

(C) Of the 21 patients in group A, who were given a second 0.75 mg/kg of Prestonal, 13 received 0.3 mg/kg of edrophonium and 8 received 0.15 mg/kg of pyridostigmine at the time when their tidal volumes had recovered to 50 per cent of the control values.

(D) Seven patients from groups A and B received 0.3 mg/kg of edrophonium when their tidal volumes reached the control values after the administration of the last dose of Prestonal.

RESULTS

The observations made on the subjects of group A are summarized in table I. All subjects in this group developed apnoea after both the initial 1.5 mg and the subsequent 0.75 mg/kg doses. The onset of apnoea was more rapid after the fractional doses than after the initial dose. In contrast to this, both the duration of apnoea and the duration of respiratory depression were shorter after the fractional doses than after the initial dose. The differences between the onset and duration of

TABLE I

The respiratory effects of Prestonal

No. of patients	Dose of Prestonal (mg/kg)	Onset of apnoea (sec)	Duration of apnoea (sec)	Duration of respiratory depression (sec)
31	1.5	88 ± 5*	310 ± 10	730 ± 34
26	0.75†	65 ± 2	271 ± 17	540 ± 30
21	0.75†	64 ± 6	262 ± 16	—

* Standard error. † Given when tidal volume returned to normal value after previous dose.

TABLE II

Comparison of the respiratory effects of Prestonal alone and when preceded by edrophonium.

Group	Drug (mg/kg)	No. of patients	Frequency of apnoea	Onset of apnoea (sec)	Duration of apnoea (sec)	Duration of respiratory depression (sec)
I.	Prestonal 0.75	10	7	80 ± 6*	175 ± 76	425 ± 48
II.	Prestonal 0.75 Edrophonium 0.30†	10	7	84 ± 8	269 ± 36	518 ± 56
	Repeat dose of Prestonal given 30 minutes after first dose.					
I.	Prestonal 0.75	10	5	67 ± 5	266 ± 63	508 ± 63
II.	Prestonal 0.75	9	6	75 ± 10	225 ± 22	516 ± 96

* Standard error. † Given 1 minute before Prestonal.

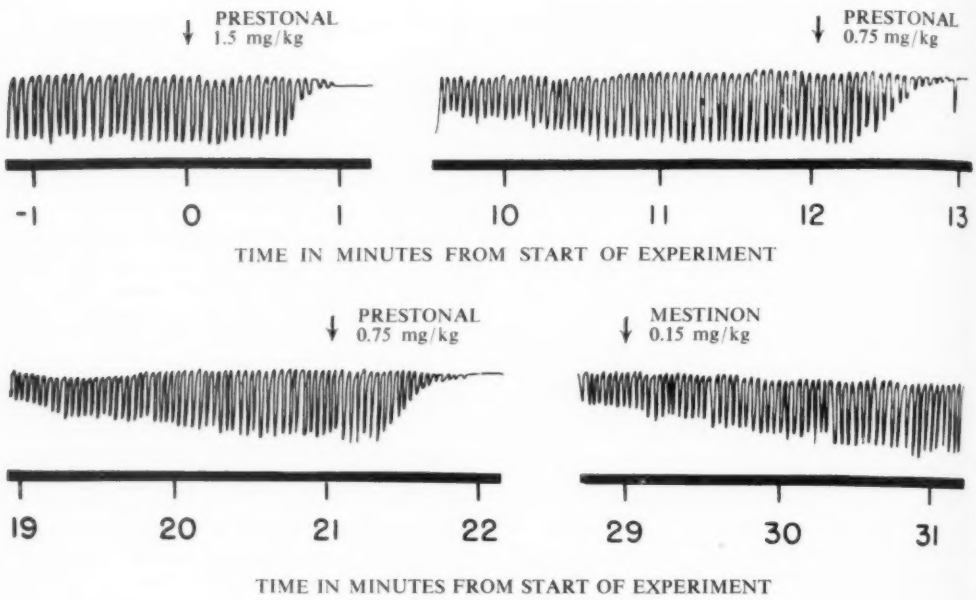


FIG. 3

The influence of pyridostigmine (Mestinon) on the respiratory effect of Prestonal. Note that 0.15 mg/kg of pyridostigmine given when tidal volume recovered to 50 per cent of control had no appreciable effect.

apnoea and the duration of respiratory depression after the first dose on one hand, and the second and third doses on the other were statistically significant. There was no significant difference between these values after the second and third doses.

The observations made on the patients in group B are summarized in table II. There was no significant difference in the incidence or onset of apnoea when 0.75 mg/kg Prestonal was administered alone (subgroup I), or preceded by 0.3 mg/kg edrophonium (subgroup II). The duration of apnoea and respiratory depression was more prolonged in the edrophonium group, but the differences were not statistically significant. The effects of a second dose of Prestonal given 30 minutes later were more marked in the group which received the first dose of Prestonal alone than in the group in which Prestonal and edrophonium were given together. Thus in subgroup I, the onset of apnoea was faster and the duration of apnoea and respiratory depression was longer than after the first dose of Prestonal. In contrast to this in subgroup II, the effects of the second dose were very similar to the first. These differences, however, were again not statistically significant.

The results obtained with the patients in group C are presented in table III. The figures in table III indicate that 0.3 mg/kg edrophonium or 0.15 mg/kg pyridostigmine administered when the respiratory tidal volume returned to 50 per cent of the control value following 0.75 mg/kg Prestonal, prolonged the respiratory depression. This prolongation was more marked (statistically significant) with edrophonium than with pyridostigmine (not statistically significant). The greater potentiating effect of edrophonium is also evident from the fact that apnoea developed in 11 of the 13 patients who received edrophonium at the

TABLE III

The influence of anticholinesterases on the respiratory effects of Prestonal

Drug (mg/kg)	No. of patients	Duration of respiratory depression (sec)	Comment
Prestonal 0.75	26	540 ± 30*	
Prestonal 0.75 Edrophonium 0.30†	13	842 ± 110	Apnoea developed in 11 patients
Prestonal 0.75 Pyridostigmine 0.15†	8	695 ± 59	No apnoea or appreciable decrease of tidal volume

* Standard error.

† Administered when tidal volume returned to 50 per cent of control value.

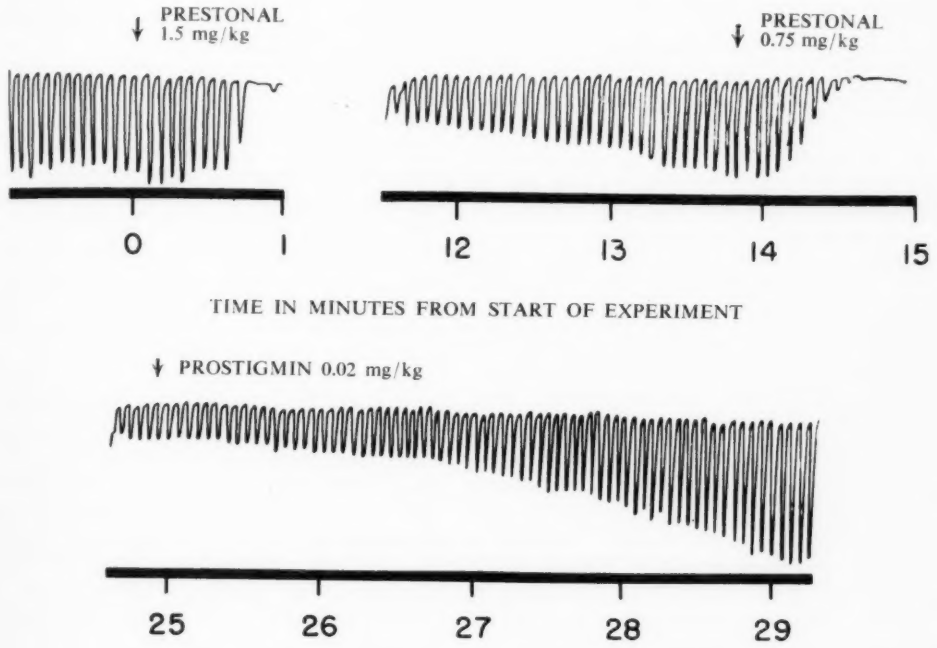


FIG. 4

The influence of neostigmine (Prostigmine) on the respiratory effect of Prestonal. Note that 0.02 mg/kg of neostigmine given when tidal volume recovered to 50 per cent of control had no appreciable effect.

time of 50 per cent recovery. No apnoea or visible diminution of the tidal volume occurred in the pyridostigmine group. The difference in the effect of edrophonium and pyridostigmine on tidal volume after 50 per cent recovery following Prestonal is also evident in figures 2 and 3.

The effect of 0.02 mg/kg neostigmine given after 0.75 mg/kg doses of Prestonal at the time of 50 per cent recovery of tidal volume was observed on 2 patients. Here again, though no immediate diminution of tidal volume could be observed after neostigmine (fig. 4), the duration of respiratory depression was somewhat prolonged in both patients.

Of the 7 patients in group D who received 0.3 mg/kg edrophonium when their tidal volumes returned to the control value following the Prestonal, 2 developed apnoea (fig. 3) and in the remaining 5, there was a 70 to 95 per cent reduction of the tidal volume within 30 to 60 seconds. Their tidal volumes returned to the control values in an average of 235 seconds.

Side Effects.

A moderate fall in blood pressure, often accompanied by a rise in pulse rate, was seen in some of the patients who received the 1.5 mg/kg dose of Prestonal. These changes were of short duration and never serious enough to give cause for anxiety. A few patients also showed marked flushing of the skin of the head, neck, and arms after the 1.5 mg/kg dose of Prestonal. This was also noted by earlier workers who recommended that Prestonal should not be administered faster than 2.0 mg per second (Frey, 1955).

DISCUSSION

The mg/kg potency of Prestonal is of the same order as that of gallamine. Its duration of action is relatively short, and lies between those of suxamethonium and decamethonium. The duration of apnoea after moderate (0.75 mg/kg) doses is about 3 minutes and the duration of respiratory depression is about 7 minutes. Doubling the size of the dose increases the duration of apnoea to about 5 minutes, and the duration of the respiratory depression to about 12 minutes.

Prestonal has less cumulative effect than the nondepolarizing muscle relaxants, e.g. d-tubocurarine or gallamine. The administration of a second 0.75 mg/kg dose of Prestonal, 30 minutes after the first dose, has only slightly greater effect on the tidal volume than the first dose (see table II). It is not known whether this relatively low cumulative effect is due to rapid excretion, breakdown or some other factor. Although Prestonal is a fairly potent inhibitor of both human plasma cholinesterase ($1_{50} = 7.3 \times 10^{-6}$ mol/l.) and red cell cholinesterase ($1_{50} = 10^{-5}$ mol/l.) (Foldes et al., 1956) it is not hydrolyzed by either of these enzymes.

The finding that a 0.75 mg/kg dose of Prestonal given immediately after recovery from the effects of a 1.5 mg/kg dose has the same effect as the second of two 0.75 mg/kg doses given 30 minutes apart (see tables I and II) suggests the possibility of desensitization or "tachyphylaxis" which is more marked after the larger initial dose. This phenomenon has been described previously with decamethonium (Pelikan et al., 1950; Unna et al., 1950) and demonstrated with suxamethonium both in laboratory animals (Foldes et al., 1956) and in man (Poulsen and Hougs, 1956).

The advantages of relatively short duration of action and moderate cumulative effect offered by Prestonal are partially offset by the fall in blood pressure and other signs of histamine release observed during its use. A further disadvantage is that when endotracheal intubation is attempted after apnoeic doses of Prestonal have been given the muscles of the jaw and larynx are frequently found to be incompletely relaxed.

The marked potentiating effect of edrophonium, and the absence of any antagonism by pyridostigmine or neostigmine on its neuromuscular action, indicate that contrary to expectations, Prestonal is a depolarizing and not a nondepolarizing muscle relaxant. The lengthening of the distance between the two quaternary nitrogen atoms and the substitution of one of the methyl groups on both quaternary nitrogen atoms by methylcarbopropoxy groups has only resulted in a marked increase in the concentration of Prestonal required at the myoneural junction as compared with decamethonium and has failed to convert it from a depolarizing to a nondepolarizing agent.

The findings of the present study also furnished some information on the duration of action of

edrophonium. The observation that the respiratory depression produced by the intravenous administration of 0.3 mg/kg edrophonium after full recovery from the respiratory effect of Prestonal was less than 4 minutes (fig. 2) emphasizes again the relatively short duration of action of edrophonium. This short duration of action was also shown by the finding that when administered one minute before Prestonal (see table II) its potentiating effect was only moderate. The lack of greater potentiation under these circumstances was undoubtedly due to the fact that the effect of edrophonium wore off before the effect of Prestonal, and consequently its activity was disguised by that of the latter.

SUMMARY

(1) The effects of Prestonal on the tidal volume of 51 patients were investigated.

(2) The duration of action of Prestonal was found to be between those of suxamethonium and decamethonium. 0.75 mg/kg Prestonal caused apnoea lasting about 3 minutes in most subjects. The duration of respiratory depression after this dose was about 7 minutes. 1.5 mg/kg Prestonal caused apnoea of 5 minutes and respiratory depression of about 12 minutes duration.

(3) Prestonal was found to have relatively little cumulative effect.

(4) A transient fall of blood pressure and flushing of the skin were occasionally seen following intravenous administration of 1.5 mg/kg Prestonal.

(5) The respiratory effects of Prestonal were markedly potentiated by the subsequent intravenous administration of 0.3 mg/kg edrophonium. The potentiating effects of neostigmine and pyridostigmine were less marked.

(6) The effect of edrophonium, pyridostigmine and neostigmine on the myoneural effects of Prestonal indicated that this compound produced a depolarization block in man.

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HYPOTHERMIA FOR CARDIOVASCULAR SURGERY: ACIDOSIS IN THE REWARMING PERIOD

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BLOOD gas changes and the related alterations in acid-base balance at lowered body temperatures have been extensively studied (Rosenhain and Penrod, 1951; Swan et al., 1953; McMillan et al., 1955; Axlerod and Bass, 1956). However, the changes associated with rewarming have evoked less interest, although most centres have encountered clinical problems during this period.

Metabolic acidosis has been reported in surface cooled hypothermic patients (Dill and Forbes, 1941) and in dogs, both during and after immersion hypothermia (Deterling et al., 1955). Brewin et al. (1955a, 1955b, 1955c, 1956) have published results of an intensive experimental study of metabolic acidosis, occurring in dogs rewarming after extracorporeal veno-venous cooling. They report evidence of metabolic acidosis found in patients recovering from cardiac surgery, after cooling by the same method.

Our experience has been outlined lately (Key, 1956), and a more detailed analysis of the biochemical findings is intended for the near future (Waddell et al., in press).

The purpose of this paper is to describe, in some detail, cases of acidosis encountered in clinical hypothermia and to comment on the anaesthetic and rewarming techniques employed. Using a standard anaesthetic technique, a high incidence of acidosis has been encountered in the rewarming period. On changing this technique, the incidence of acidosis fell markedly and it is proposed to present this material in the following manner:

(1) Introduction.

(2) A brief description of the original anaesthetic technique, giving details of each of the cases which became acidotic.

(3) A brief description of the current anaesthetic technique, outlining those cases which have become acidotic.

(4) A discussion of the factors involved, including the differential diagnosis of the causes of acute acidosis in the rewarming period.

INTRODUCTION

The problems to be presented are from a consecutive series of patients submitted to hypothermia.

Methods.

The technique for inducing hypothermia in this unit has been described (Bigelow et al., 1950, 1954), and consists essentially of surface cooling.

Blood sampling has proven technically difficult in cold patients. Arterial blood was preferred but, in a few instances, venous was accepted.

pH determinations have been performed on seventy-two consecutively drawn arterial and venous samples representing a pH range of 7.00 to 7.60 units and a temperature range from 38°C to 29°C. The venous value was never higher than the arterial and the difference was found to be greater at the alkalotic end of the range. Thus:

26 samples, giving values under 7.35 units (arith. mean 7.25 units), showed an average a-v difference of 0.026 pH units.

22 samples, giving values between 7.35 and 7.45 units (a.m. 7.40 units), showed an average a-v difference of 0.043 pH units.

24 samples, giving values over 7.45 units (a.m. 7.52 units), showed an average a-v difference of 0.069 pH units

In the ensuing case reports, the majority of pH values were from arterial blood. When venous blood only was available, such values will be corrected, for the sake of simplicity, utilizing the above information. Correction factors: venous pH <7.35 units $+0.03$: venous pH $7.35 - 7.45 + 0.04$: venous pH >7.45 units $+ 0.07$.

Whole blood pH was determined in a Beckman pH meter, within five minutes of sampling, at $24°C \pm 1°C$. The value obtained was corrected for the patient's rectal temperature, from the formula $pH = pH_o - 0.0149 (T_r - T_o)$ (where pH_o is the pH read at temperature T_o and T_r is the patient's rectal temperature) (Graig et al., 1952).

GROUP A

The anaesthetic technique was similar in each of this group of patients. These cases were premedicated with morphine or papaveretum and hyoscine. Induction was with 2.5 per cent thiopentone sodium and intubation performed after giving intravenous suxamethonium. d-Tubocurarine was used to permit controlled respiration and to abolish shivering. The patients were ventilated with nitrous oxide and oxygen, using to and fro absorption. Ventilation was controlled manually in the earlier cases and by a positive-negative pressure Jefferson ventilator in the later cases.

The patients were placed between Therm-o-rite blankets with ice bags applied to neck, axillae and groins and, in some cases, with crushed ice applied to trunk and thighs. Cooling was discontinued at a point where the estimated drift would achieve the desired temperature. The top blanket, ice bags and ice were removed, circulation of the refrigerant stopped and the operation started with the patient lying on the bottom cooling blanket.

Rewarming was often started during the operative period by circulating fluid, at 34°C to 38°C, through the bottom blanket. At the end of the procedure, the patient was dried, returned to bed with a few hot water bottles (at 38°C), and covered with two or three light warmed blankets.

An anticholinesterase was given in dosage sufficient to ensure adequate spontaneous respiration and, coincidentally, to promote shivering.

Case Reports

CASE 1. Mrs. N. C. Age 28.

Diagnosis. Tetralogy of Fallot with cyanosis and left heart failure.

Operation. Open infundibular resection was performed at 29°C while circulation was interrupted for seven minutes.

Rewarming. Shivering was noted intermittently. The rewarming period was not remarkable until T_r reached 33.9°C.

pH. After a pre-operative value of 7.30_c (pH_c = corrected value), the pH during cooling and operation ranged between 7.38 and 7.48 units. During the early rewarming period the pH declined gradually to 7.20.

Rewarming acidosis. At T_r 33.9°C, the patient suddenly lost consciousness and ceased active movement: respiratory movements, hitherto considered perfectly adequate, were depressed, necessitating controlled respiration. No fall in blood pressure was noted. pH was 7.00 units. Decamethonium 3 mg was given to permit more vigorous hyperventilation, when the pH had fallen to 6.95 during 15 minutes' controlled respiration. After 15 minutes' hyperventilation, the pH had risen to 7.07 units and the patient soon regained consciousness, began to breathe spontaneously and move actively. The pH, after clinical recovery, was 7.12 units.

Observation was continued but no further complications were noted during rewarming. Respiratory excursions remained adequate and the pH showed a gradual rise.

Remarks. Serum sodium values, obtained for another study, were within normal limits throughout cooling, but on rewarming to T_r 37°C the level was 117 m.equiv/l.

This was the first case of severe acidosis detected in the rewarming period and its reversal was originally attributed to hyperventilation. It is now appreciated that muscular relaxation contributed to this reversal.

CASE 2. Mrs. F. D. Age 30.

Diagnosis. A.s.d. and congestive heart failure.

Operation. Perauricular digital exploration of the right atrium and interventricular septum was carried out. The circulation was not interrupted since her lesion was not considered amenable to surgery. The lowest temperature reached was 28°C.

Rewarming. Rewarming was started during operation and continued between the Therm-o-rite blankets until the patient was transferred to bed at T_r 33.5°C. She was extubated, after breathing well without assistance for two hours, at T_r 34°C. Shivering was not

noted at any time. The postoperative course was smooth until the temperature was close to normal.

pH. The pre-anaesthetic level was 7.43$_e$. Subsequently, the pH rose to 7.55 during operation, then ranged gradually down to 7.26 at T_r 36.4°C.

Rewarming acidosis. At T_r 36.6°C., the pH was 7.12 units and respiration was assisted for 15 minutes before the patient lost consciousness, at pH 7.03. Associated with the loss of consciousness were loss of virtually all respiratory activity, cessation of active movement, fall in systolic blood pressure and a rise in heart rate.

Despite vigorous hyperventilation with muscle relaxant, 1,000 ml of citrated blood and 5 grams of $NaHCO_3$, the pH continued to fall and consciousness and respiration remained depressed. Blood pressure was partially restored, temporarily, but systolic levels were not raised above 80 mm Hg. The tachycardia persisted and, after increasingly frequent ventricular premature beats, irreversible ventricular fibrillation supervened. The last pH obtained before death was 6.80 units.

Remarks. Acidosis must be implicated in this woman's death although severe heart disease was certainly contributory and blood replacement may have been somewhat inadequate.

The sodium level during the profound acidosis —and prior to the $NaHCO_3$ infusion—was 125 m.equiv/l. Previous values were within normal limits.

CASE 3. Master R. L. Age 15.

Diagnosis. Tetralogy of Fallot with cyanosis and left heart failure.

Operation. A Blalock procedure was performed, without incident, at T_r 31°C.

Rewarming. Rewarming was entirely spontaneous and was uneventful until the temperature had risen to T_r 36°C, when the patient was fully conscious.

pH. The pre-anaesthetic level was 7.39$_e$. A rise to 7.63$_e$ was noted during cooling and operation. During early rewarming the pH declined to the "control" level.

Rewarming acidosis. At T_r 36°C, the pH was 7.19$_e$ units. Decamethonium 3 mg was given intravenously and vigorous hyperventilation was started. Within five minutes, consciousness was lost. There was associated hypotension and tachycardia and it was noted that the pH had fallen to 7.13$_e$ units.

Hyperventilation was continued and a 1 per cent $NaHCO_3$ infusion started at a rapid rate. Improved level of consciousness was noted within ten minutes and the pH had risen to 7.20$_e$ units. The rate of $NaHCO_3$ infusion was slowed.

At T_r 37.5°C, the pH was 7.29$_e$ units. 2.5 grams of $NaHCO_3$ had been given. The patient was again fully conscious, breathing well, reacting to the endotracheal tube and moving actively. His condition remained good and the pH showed a slight further rise.

Remarks. Depression of consiousness in this case was apparently due to a moderate acidosis. Clinical recovery seemed related to the $NaHCO_3$ infusion.

CASE 4. Mr. H. L. Age 22.

Diagnosis. Aortopulmonary window with cyanosis and congestive failure. Possible septal defect.

Operation. Perauricular digital exploration revealed a v.s.d., which was considered inoperable under hypothermia. The lowest temperature reached was 30°C.

Rewarming. The bottom blanket was warmed during operation but external heating was stopped at T_r 32.3°C, when the patient was transferred to bed. Rewarming was complicated by unusual ventricular irritability. Attempted hyperventilation was associated (with the thorax closed) with frequent ventricular extrasystoles and could not be maintained. Procaine amide, intravenously, did not reduce cardiac irritability. Gross shivering was noted.

pH. After a pre-anaesthetic value of 7.33$_e$ units, the pH varied between 7.44 and 7.56 units during cooling and operation, then fell to 7.24$_e$ during rewarming.

Rewarming acidosis. At T_r 34°C, $NaHCO_3$ 5 per cent was given, intravenously, in a 50 ml dose, because the pH had declined to 7.24 and cardiac irritability prevented hyperventilation. This produced elevation of the heart rate and blood pressure without changing the pH trend. The pH had fallen to 7.03 units by the time the temperature had risen to 36.2°C. A 2.5 per cent $NaHCO_3$ infusion was started at a rate of 5 ml/min. After twenty-five minutes the pH had remained at 7.03$_e$ and the infusion rate was slowed a little. Gross shivering recurred and chlorpromazine 25 mg was given, intravenously. No clinical signs of acidosis appeared until T_r 37.5°C, when definite depression of consciousness, respiration and active movement was noted. The pH was 6.95$_e$. Respiration was assisted and the rate of $NaHCO_3$ infusion increased.

After 25 grams of $NaHCO_3$ had been given, the patient suddenly regained consciousness and once again began to breathe spontaneously and move actively, at 37.7°C. The pH was 7.18 units. Eventually, the pH stabilized a little above 7.30 and no further deviations were noted.

Remarks. The slow response of acidosis to a large dose of $NaHCO_3$ was impressive. The amount given raised the serum sodium from 146 to 148.4 m.equiv/l. The patient did not develop oedema subsequently, although an easily controlled episode of acute nocturnal dyspnoea occurred on the third postoperative night.

Comments

In the four cases of severe acidosis, sudden loss of consciousness, in hitherto conscious patients, was the most striking feature. When this occurred, pH values were found to be between 7.00 and 7.13 units.

In the few instances when CO_2 combining power estimations were made during periods of acidosis,

low values demonstrated a predominantly metabolic element in the acidosis.

Attendant upon loss of consciousness, with a falling pH, was generalized muscular weakness in patients who had previously been moving actively and breathing spontaneously and fully. With the muscular weakness, respiration became obviously inadequate and required controlled respiration in each case.

The blood pressure fell and the heart rate rose in two patients, who had not received $NaHCO_3$, at the time of onset of symptoms.

Finally, correction of the acidosis was associated with return of consciousness, resumption of adequate spontaneous respiration and active movements and with a decline in heart rate and restoration of blood pressure—this being almost as dramatic as the onset of this condition. When recovery occurred, pH values were found to be between 7.12 and 7.20 units.

The measures instituted to correct the acidosis reflect one's thinking at the time these problems were encountered.

In Case 1 respiratory acidosis was immediately suspected and hyperventilation started with a muscle relaxant. In retrospect it is probable that both hyperventilation and relaxation contributed to the correction of the pH.

Case 2 proved resistant to attempted hyperventilation (without a relaxant) and a small dose of bicarbonate.

Sodium values in the period of profound acidosis, in the first two cases, were of reassurance in the use of sodium bicarbonate in the treatment of the third case. The rapid restoration of consciousness, after a small dose of bicarbonate, was impressive, although the dosage used would not influence the pH greatly.

In Case 4 hyperventilation could not be achieved and correction of the acidosis must be attributed to the large dose of $NaHCO_3$ used in conjunction with medication to control shivering.

pH (venous values as black dots) has been plotted against rectal temperature in ten cases (fig. 1). The median curve is representative of the individual tendency in each case with some rise in pH during cooling and a fall during rewarming.

Four cases of severe acidosis, in ten cases studied, and an overall incidence of acidosis in 50 per cent of cases prompted revision of the anaesthetic and rewarming technique.

GROUP B

The aims, in the attempt to prevent acidosis during rewarming, were several fold:

(1) Maintenance of peripheral circulation throughout hypothermia.

(2) Control of respiration, during cooling and operation, in such a way as to keep the blood pH within the normal range.

(3) Abolition of shivering.

(4) Promotion of adequate spontaneous respiration as early in the rewarming period as possible.

The current technique is described elsewhere (Fairley, 1957), but, in summary, is as follows. The patient is sedated, on the night before operation, with oral promethazine. Promethazine and chlorpromazine are given intramuscularly one hour pre-operatively. Induction of anaesthesia is achieved with an intravenous infusion of chlorpromazine, promethazine and pethidine, administered over 15–30 minutes. This is usually sufficient to abolish the eyelash reflex, but has not proved an embarrassment in patients with severe heart disease. Relaxation is provided, for intubation, by suxamethonium and these patients are ventilated with nitrous oxide-oxygen, by the Jefferson ventilator, using d-tubocurarine intermittently. Control of a rising pH is achieved by taking the soda lime out of the circuit and, in some cases, by reducing the flow of gases.

The cooling technique is identical to that previously employed.

Shivering during rewarming is controlled by intravenous or intramuscular chlorpromazine.

Spontaneous respiration during rewarming is promoted by the use of an anticholinesterase, whenever indicated.

It was originally planned to rewarm the patient, when possible, by the use of warm fluid circulated through the blankets and by hot water bottles. However, many of the second group of patients had no more active measures for rewarming than the former.

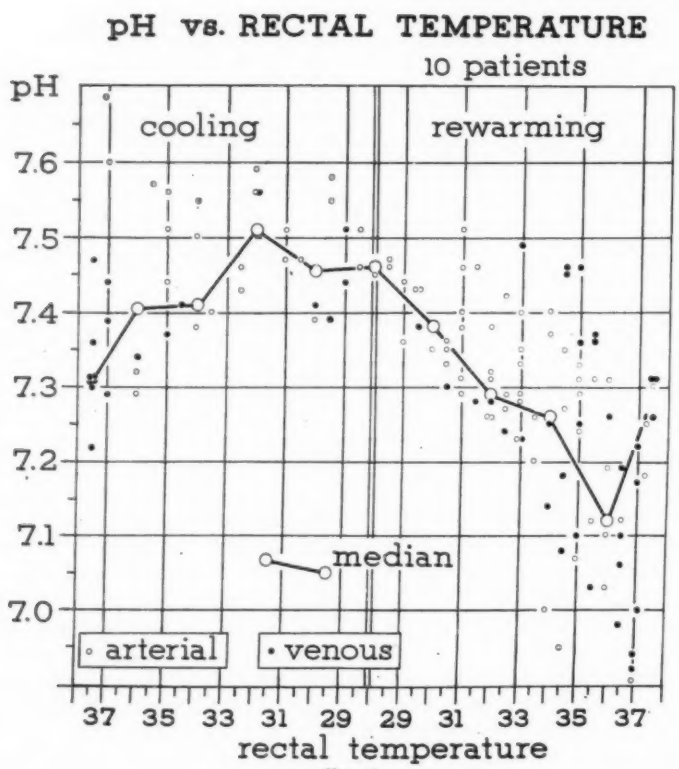

FIG. 1

Case Reports

CASE 5. Master C. B. Age 16.

Diagnosis. Fallot's tetralogy with cyanosis and congestive heart failure.

Operation. Transventricular infundibular resection was performed, at T_r 29°C, with seven minutes' circulatory occlusion. Ventricular fibrillation followed cardiac massage, instituted for poor heart action, after the circulation was restored.

Rewarming. Rewarming was initiated during surgery, by warming the bottom blanket, and was continued between the Therm-o-rite blankets until the patient was transferred to bed, at T_r 31.7°C. No further external heating was used because of moderate hypotension. The patient was extubated at T_r 32.5°C, when reacting violently to the endotracheal tube. Shivering was not noted. He was fully conscious, talking rationally, breathing adequately and moving well at 33°C. Heart rate and blood pressure were satisfactory at this point.

Shortly after reaching T_r 33°C, he became hypotensive and plasma expander was given, while awaiting more whole blood. The level of consciousness declined gradually and manual control of respiration was started. The blood pressure could not be maintained despite further blood and plasma expander. He developed cardiac arrest at T_r 34.5°C. The chest was opened but attempted resuscitation was not successful.

pH. The pre-anaesthetic pH was 7.44_e and subsequent samples within normal limits. The first postoperative samples were 7.31_e and 7.28_e and chlorpromazine 50 mg was given, despite the absence of shivering. Prior to the depression of consciousness, the pH declined to 7.24_e units.

Rewarming acidosis. Significant acidosis was found at 33.4°C, when the pH was 7.19_e units.

Remarks. This case was in acidosis due to oligaemic shock and, in retrospect, chlorpromazine was not indicated.

pH values below 7.25 have been found in two other cases:

CASE 6. A 25-year-old woman, severely disabled with an a.s.d. and pulmonary stenosis, developed a moderate acidosis—with no clinical manifestations—after circulatory interruption of four minutes, for open pulmonary valvotomy at T_r 29.2°C. She had

four episodes of ventricular fibrillation, lasting between two and ten minutes, but sinus rhythm was eventually restored. Rewarming was uncomplicated, despite a pH reading of 7.18_e at 31.2°C. There were no clinical signs of acidosis and the pH rose without measures to correct the imbalance.

CASE 7. Finally, several values below 7.25 were obtained (7.17_e–7.23_e) during rewarming in a patient in whom the complicating factor was minimal residual curarization (in an abdominal aortectomy, with very low urinary output). This patient was semicomatose for a prolonged period but did not show the sudden loss of consciousness associated with severe acidosis in the earlier cases. Neostigmine and atropine had been given at the time of finishing the operation but the acidosis was not reversed until a further dose was given, some time later, with subsequent spontaneous hyperventilation. He made an uneventful recovery.

Comments

The pH values have been plotted against the rectal temperature, at the time of sampling, in 19 patients (fig. 2). Again, the median represents the usual tendency with some rise during cooling and a gradual decline during rewarming. In many instances this is followed by a second rise, giving a sinusoidal curve, and often rising above the pre-operative value.

A pH below 7.14 has not been observed, in the second group of patients, nor has the "acute acidotic syndrome of rewarming" been encountered.

Rewarming rates. Several variables were introduced with the modifications described, but it is instructive to compare the rewarming rates in the two groups. The rewarming rate of the first group, expressed in degrees centigrade/hour/70 kg body weight, ranged from 0.47°C to 3.49°C. The arithmetic mean was 1.82°C and the standard deviation 0.98. The range in the second group was 0.78°C to 1.99°C/hour/70 kg. The arithmetic

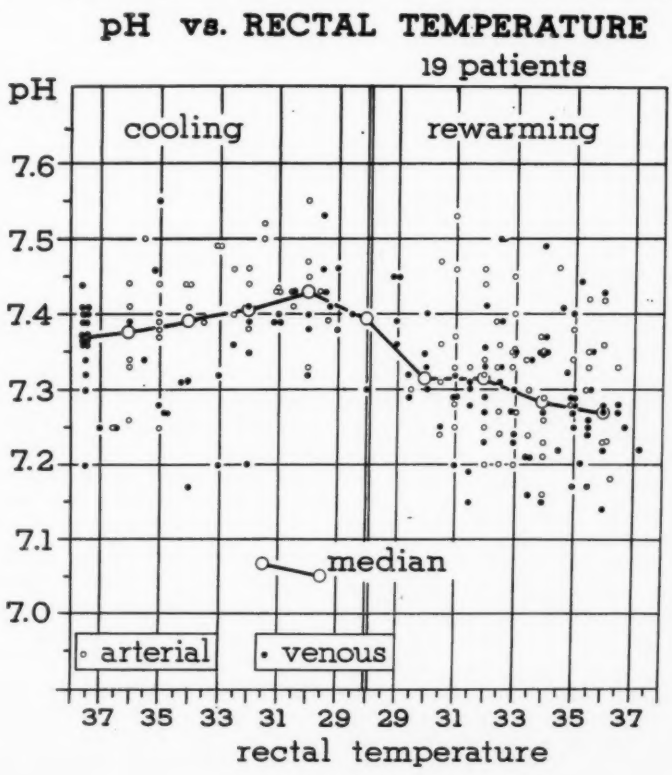

FIG. 2

mean was 1.34°C and the standard deviation 0.31. The difference between the means is significant at the 5 per cent level. This may be attributed to depression of shivering (in group B). The use of chlorpromazine is an important factor in the control of shivering but somewhat greater use of external heat may have been a contributory factor.

DISCUSSION

Without elaborating on the many factors involved in the maintenance of acid-base balance, it is evident that in hypothermia by surface cooling, using controlled respiration, the following influences exist:

(1) Lack of spontaneous respiratory compensatory mechanisms.

(2) Peripheral vasoconstriction due to cold and to respiratory alkalosis, should the latter be allowed to occur.

(3) Shivering and increased muscle tone, with resulting rise in lactates and other acid metabolites in the blood.

(4) Probable depression of renal control of hydrogen ion concentration.

The cases in group A would appear to have been exposed to these influences, since, with an anaesthetic technique commonly used in thoracic surgery, a high incidence of acidosis was encountered in the rewarming period. Reference to the results of the Toronto General Hospital neurosurgical team (also using surface cooling) showed that their anaesthetic technique for hypothermia (Vandewater et al., 1955) did not produce a rewarming acidosis (Vandewater, 1957). By the use of (1) spontaneous respiration, (2) antishivering agents, and (3) peripheral vasodilators, they were able to circumvent respiratory alkalosis and metabolic acidosis, to a large extent. They commonly observe a slight rise in pH during cooling and a fall of similar proportions during rewarming.

Alkalosis. There are several theoretical objections to alkalosis during cooling, viz., shift of the oxygen dissociation curve to the left, peripheral vasoconstriction and, possibly, renal discard of sodium bicarbonate, etc. An attempt has been made to keep the blood pH within normal limits in group B. The methods used have been mentioned. Figure 2 shows fewer readings above 7.45 and demonstrates some measure of success.

Chlorpromazine. This agent offers practical and theoretical advantages in facilitating cooling (Dundee et al., 1954), inhibiting shivering and maintaining peripheral circulation. Peripheral vasoconstriction is considered deleterious in that it may foster peripheral hypoxia, with consequent promotion of anaerobic glycolysis and increased lactate production. This is a similar mechanism to that producing lactate accumulation in oligaemic shock (Wiggers, 1950). Chlorpromazine is used to prevent gross shivering during the rewarming period, in an attempt to prevent the sudden massive production of lactates and other acid metabolites of muscular catabolism. Depression of shivering maintains anion production within limits which can more readily be controlled, by the compensatory hyperventilation of the spontaneously breathing postoperative patient, provided there is no gross pulmonary pathology present.

The simultaneous introduction of more than one variable, in the more recent anaesthetic technique, prevents any comment as to the relative importance of the various factors operative in this method. However, it is believed that the prophylaxis of this technique, against the acute acidotic syndrome of rewarming, is to be preferred to the necessity of undertaking the active therapy of this condition.

Differential diagnosis of rewarming acidosis.

From the discussion of the factors involved, it is evident that a low blood pH, in the rewarming period, could be due to any of several factors:

(1) Metabolic acidosis. This has been discussed above the cases 1–4 are representative.

(2) Respiratory acidosis. The similarity between the metabolic acidosis of rewarming, described above, and the respiratory acidotic syndrome reported by Scurr (1954) is remarkable. Adequate spontaneous respiration, in the rewarming period, is invaluable, as a means of combating impending metabolic acidosis, and it should be noted that, following the use of relaxant agents, ventilatory power which normally would be adequate may be incapable of the hyperventilation necessary for this compensation. This was seen in case 7.

(3) Haemorrhage. The low pH values obtained in haemorrhagic shock are well recognized (Bland,

1956) and may cause differential diagnostic confusion in cardiovascular surgery. This was seen in case 5. Massive transfusion, with resulting increase in citrate radicles, will contribute to the acidosis (Brewin and Neil, 1954; Yendt, 1957).

(4) Peripheral embolism. One has seen a case of gross metabolic acidosis, resistant to therapy, occurring in a patient who sustained multiple peripheral emboli (including an aortic saddle embolus), when an atrial myxoma was encountered unexpectedly. This was presumably due, in part, to peripheral anoxic metabolism.

Treatment of the acute acidotic syndrome.

Some decline of the blood pH level, in the rewarming period, is to be expected in the majority of cases. However, this level rarely falls below 7.30 units. Should readings continue to drop and signs of the acute acidotic syndrome develop, this should be considered an emergency situation.

From the discussion of the differential diagnosis, it will be evident that more than one factor may be contributing to the acidosis. Thus, although accumulation of acid metabolites is the probable cause of the falling pH, consideration should be given to the respiratory exchange and to blood volume, etc. Whatever the cause of the acidosis, a muscle relaxant will permit hyperventilation through soda lime and the resulting reduction in plasma CO_2 will temporarily reverse the falling pH level.

If shivering has occurred, chlorpromazine 25–50 mg should be given intravenously and, in extreme cases, an intravenous infusion of sodium bicarbonate should be started. Careful and frequent observations of blood pH levels should be used as the clinical yardstick, as to the efficacy of the therapy; in addition, total blood CO_2 or alveolar CO_2 levels may be of assistance. It is felt that while dosage of bicarbonate may be calculated from widely recognized formulae, the latter were designed for the treatment of diabetic ketoacidosis, which is probably not analogous to the complex circumstances of recovery from cardiovascular surgery under hypothermia. Therefore, it is safer to adjust the dosage according to the blood pH response.

Any treatment of an acute metabolic acidotic crisis is aimed at tiding the patient over his temporary inability to maintain a normal H-ion concentration, in the presence of gross lactate accumulation.

It is of interest to note that the acute acidotic syndrome occurred in patients who had neared normal temperature. Because of this, temperature should not be used as a yardstick of fitness for return to the ward. Experience has shown that a rising pH is the best index of the patient's well-being in the rewarming period.

In retrospect, cases of sudden death during rewarming, or others exhibiting a nonspecific picture of hypotension and impaired consciousness, prior to restoration of normal body temperature, may have been acidotic. It is possible that the occasionally described, rather vague conditions, " rewarming shock " and " rewarming death " may be explicable on a basis of metabolic acidosis.

SUMMARY

A report has been made of a series of cases in which severe metabolic acidosis arose, during the rewarming period following hypothermia for cardiac surgery. A further series is reported, showing that this syndrome is not encountered when care is taken to avoid (*a*) shivering, (*b*) peripheral vasoconstriction, (*c*) respiratory alkalosis during cooling and operation, and (*d*) when spontaneous respiration is established at the earliest opportunity, postoperatively.

The differential diagnosis of the causes of severe acidosis in the rewarming period and the treatment of the acute acidotic syndrome are discussed.

ACKNOWLEDGMENTS

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BOOK REVIEW

Cleft Lip and Palate (2nd edition). By W. G. Holdsworth. Published by William Heinemann (Medical Books) Ltd., London, 1957. Pp. 187; illustrated. Price 42*s*.

This new edition of W. G. Holdsworth's book on cleft palate and hare lip surgery is a further improvement on the excellent first edition. The chapter on development by Professor Richard Harrison makes interesting reading, but the parts which are, of course, of most importance to anaesthetists are the three chapters on pre-operative management of the infant, on general anaesthesia for these cases, and on postoperative care. The chapter on general anaesthesia is, as before, by Drs. George Ennis and D. A. Sherman, and they are to be congratulated on the clear and concise way in which they describe their technique. There is no doubt that the special experience, both surgical and anaesthetic, that is acquired in the plastic surgery units has contributed to the greatly lowered morbidity and mortality of lip and palate surgery. There is much to be said for and against segregation of special cases into special units, but the writer feels that there is an unanswerable argument for allowing these babies to receive the full benefit of the techniques developed and practised in the plastic surgery hospitals (and in a few paediatric hospitals). The anaesthetist will find much of importance and interest in the chapters on pre- and postoperative assessment and care. Professor T. P. Kilner and the late Dr. John Hunter performed many thousands of operations and anaesthetics for hare lip and cleft palate without a death and this result was partly achieved by the co-operation as a team of the surgeon, anaes-

[*Continued on page* 333

Brit. J. Anaesth. (1957), **29**, 319

GENERAL ANAESTHESIA IN OPHTHALMIC SURGERY

BY

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MANY ophthalmic operations can be performed under local analgesia and this technique is used with satisfaction in all parts of the world today; in fact many surgeons and consultant anaesthetists are satisfied that the best results are obtained by this method. On the other hand, general anaesthesia is used much more than formerly and in some centres it is used routinely for most operations, including removal of cataracts. There are, in addition, occasions when the future of the eye depends upon surgery which can only be performed under general anaesthesia; but if this is not skilfully administered a functionless eye may result from coughing and vomiting. Having watched the surgeons in this area make a slow but continuous change-over during about five years, I feel that it is opportune to review the value of general anaesthesia in ophthalmic surgery and to discuss ways to produce maximum benefit for patient and surgeon.

THE DISADVANTAGES OF LOCAL ANALGESIA

The less desirable aspects of locals must be considered before advantages can be claimed for other techniques. Some of these are:

(1) *The co-operation of the patient* is essential for success and so difficulties arise in:

(*a*) The young (under 12) and this includes most cases of squint.

(*b*) The very old.

(*c*) The disabled, deaf, arthritic, etc.

(*d*) Those who are temperamentally unfit or very nervous.

(2) *A greater strain* falls on the surgeon because he has to bolster the morale of the patient as well as operate. With a difficult patient this strain can affect an apprehensive surgeon to the extent of reducing his skill; these surgeons, and there are many of them, are happier when their patients are unconscious. This may be one of the greatest advantages of general anaesthesia in ophthalmic surgery.

(3) *Technical difficulties.*

(*a*) Facial block.

(i) If inadequate, "squeezing" may occur with its accompanying dangers.

(ii) Pain in the temporo-mandibular joint for some weeks afterwards.

(iii) On rare occasions prolonged facial paralysis.

(*b*) Topical analgesia before an operation may upset the patient: there is a slight risk of introducing sepsis to the outer eye.

(*c*) Iris anaesthesia (retrobulbar injection into the ocular muscular cone).

(i) May not give complete analgesia particularly in cases of acute glaucoma.

(ii) Risk of retrobulbar haemorrhage which necessitates postponing the operation for a week.

(iii) The inferior rectus muscle may be paralysed by the injection, in which case the patient cannot look down and the operation is made more difficult.

(iv) Intra-ocular pressure is often lowered excessively and renders operations like trephine, iridectomy ab externo and extracapsular lens extractions much more difficult.

(*d*) Postoperative vomiting, though less common than after general anaesthesia, can occur.

(4) *Personal preference.* There is little doubt that most people prefer to be asleep when surgery is being performed on them. I have had a number of patients who have had previous eye operations

(mainly for cataract) whilst awake; pre-operatively most have stated that they were quite satisfied last time, though later they were loud in their praise of general anaesthesia. One such patient surprised me by giving as her reason for this enthusiasm "that this time I did not feel anything." Some on hearing that they would be asleep have expressed great relief that "they would not have to go through that again." There have been a few who preferred the local and their reason has always been the same—they had vomited after the general but not after the local.

(5) *Insufficient experience for the anaesthetist with general anaesthesia* for intra-ocular operations will mean that the surgeon will not receive all possible help from him on the occasions when anaesthesia is essential for intra-ocular surgery. Good vision is unlikely to be obtained from a second operation necessitated by failure at the first one. Poor results mean little or no vision in that eye.

ADVANTAGES OF GENERAL ANAESTHESIA

Patient's Choice. As has already been stated most people prefer to be asleep during the performance of anything but very minor surgery.

Surgeon's Choice. If a patient is asleep there is no doubt that it is easier for the general management of a theatre. The teaching of surgical techniques can be very disturbing to the conscious patient. Also, as has been mentioned above, many surgeons have an even greater reason for wanting their patients to be asleep.

DISADVANTAGES OF GENERAL ANAESTHESIA

Patient's View. The only patients who have commented adversely on the method are those who have vomited. Whilst this incidence can be kept at about 5 per cent in adults, it is doubtful if it can be eliminated.

Nursing. A conscious patient will almost certainly need less nursing care than one who is, or has been, unconscious. Many patients in the ophthalmic wards are edentulous and must be watched carefully during recovery of consciousness. Consequently these cases do need more care than the local group, but no one has suggested that this created a need for extra staff.

TECHNIQUES

Before describing any techniques for particular operations one must consider two important aspects of this work:

(1) The necessity for an almost bloodless field.

(2) The control of intra-ocular tension.

BLOODLESS SURGICAL FIELD

The advantages of a bloodless field are greater ease of operating and a less stormy convalescence. It should be possible to have a "white eye" in most cases; obvious exceptions are those which are red, inflamed or congested by the pathological condition for which the surgery is being performed. The following points are thought to be important in preventing the eye from becoming engorged during anaesthesia.

(1) *Induction.* A smooth induction followed by smooth maintenance and recovery are essential for good results in intra-ocular surgery.

(2) *Agents.* It always will be true that it is the anaesthetist who produces results rather than the agents that he uses; nevertheless I do not use gallamine hydrochloride in this work, because not only my own cases but those of others appear to bleed more when relaxants other than those mentioned below are used for a routine technique. Suxamethonium chloride is used for patients who are to breathe spontaneously and tubocurarine hydrochloride when respiration is to be controlled. Bleeding is increased if respiration is not assisted after the administration of the longer acting relaxants.

(3) *Apparatus.* If respiration is to be spontaneous, resistance to air flows should be carefully eliminated. Children have some form of T-piece technique. A lightly loaded valve or Bullough's (1952; 1955) technique is used for adults. If for any reason it is necessary to alter the tension on the expiratory valve of a Magill's assembly, one's hand must pass under the sterile towel in the area where the surgeon's swabs and instruments lie; this inconvenience is avoided if a circle absorber is used. Then not only is the expiratory valve readily accessible but one can easily change from closed to semi-open or T-piece technique.

(4) *Posture.* A head up tilt of the table helps to produce a bloodless field in three ways:

(*a*) Improved venous drainage of the eye.

(*b*) This position, particularly during general anaesthesia, tends to lower the systolic blood pressure and so the volume of blood reaching the eye per minute.

(*c*) The pressure of the abdominal viscera on the diaphragm is reduced, particularly in obese subjects, which in turn improves pulmonary ventilation and the venous return to the heart. This must assist the venous drainage of the eye.

(5) *Lamellae.* Tablets of adrenaline hydrochloride (0.5 mg) help in the production of a "white eye." These, however, cause discomfort and so should be used after the induction of anaesthesia. Full surgical sterility should be observed when placing these in the eye. Guttae adrenaline 1/1000 are also satisfactory.

THE INTRA-OCULAR PRESSURE

The eye may be looked on as a chamber containing fluid enclosed within a feebly distensible envelope formed by the sclera and cornea. The pressure within is maintained at its normal height by two factors—the elasticity of the outer coat and the volume of its contents, which is maintained by the energy derived from the blood pressure.

Variations of the Intra-ocular Pressure.

The intra-ocular pressure may be varied from normal by three groups of factors:

(1) *External pressure upon the globe by voluntary muscles.* The total effect exercised upon the intra-ocular pressure by the normal tone of the voluntary muscles is demonstrated by the fact that the pressure of the eye falls to almost half of its original height when the muscles are paralysed by curare, although the blood pressure is maintained at a constant level.

(2) *Alterations in the equilibrium level.* The intra-ocular pressure varies directly with the blood pressure in the capillaries, and therefore can be influenced by the general arterial pressure and the venous pressure only in so far as their influence penetrates to the capillary circulation. When the capillary circulation remains passive, changes in the arterial pressure are reflected directly in the intra-ocular pressure. If the venous pressure is altered, other things being equal, intra-ocular pressure varies very directly with it.

(3) *Variation of the intra-ocular volume.* Since the distensibility of the envelope of the eye is very small, the intra-ocular pressure may be varied by altering the volume occupied by any of its contents. A dilatation of its capillaries brings about a large rise of pressure, and their contraction a corresponding fall.

The Control of Intra-ocular Tension during Anaesthesia.

For some operations, e.g. extracapsular extraction of lens, a normal intra-ocular tension is usually desired by the surgeon as this aids expression of the lens. If, however, at any time during any operation there is risk of vitreous loss, this risk is reduced if the tension of the eye is lowered. This risk is always present during any intra-ocular operation and particularly during cataract extractions. When the anaesthetist has a fair measure of control of the intra-ocular tension, he can provide a tension appropriate for the operation and the surgeons are very appreciative of the assistance afforded to them. In the anaesthetized patient this tension can be varied during the operation at the request of the surgeon.

Anatomy.

Figures 1 and 2 show the important difference to the anaesthetist between intra- and extracapsular operations. When the cataract has been removed without its capsule (fig. 1), the vitreous face still has this to support it. To coax the lens through the small hole in the anterior capsule it is expressed against the supporting vitreous as shown in figure 3. If the eye has good tone the pressure is effective; if, however, the eye is very soft the counterpressure is lacking and the extraction made more difficult. When the lens is removed within its capsule (fig. 2), there is practically no support for the all important vitreous and it is easily seen how increased intra-ocular tension following anaesthesia can cause the vitreous to follow the encapsulated lens as it is withdrawn.

With full understanding of the foregoing principles the experienced anaesthetist will then use

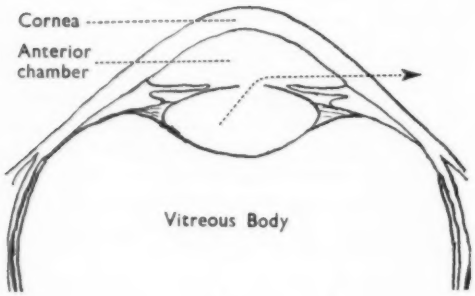

FIG. 1

Showing the eye after removal of lens by the extracapsular operation. Vitreous face is protected by the posterior capsule of the lens.

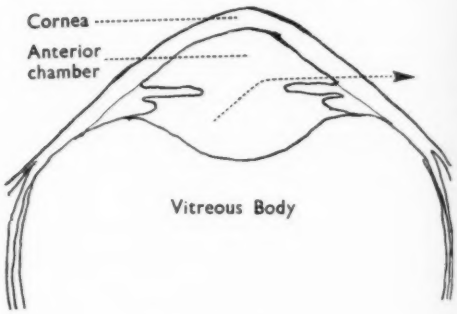

FIG. 2

Showing the eye after removal of lens by the intracapsular operation. The vitreous face is exposed and will prolapse more readily.

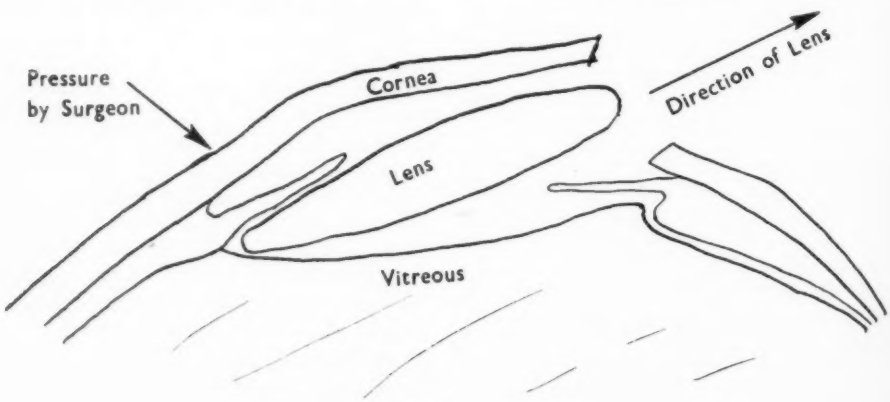

FIG. 3

Extracapsular extraction of lens. Lens is expressed between the cornea and the supporting vitreous.

the techniques which he already knows will give the required conditions. The following are the methods which I normally employ.

ANAESTHETIC TECHNIQUES

Children. The youngest (one week to one year old) have usually come for probing of the nasolachrymal duct or for examination of the eye and refraction under anaesthesia. It seems unnecessary to intubate these cases, yet even the smallest face piece (Sandiford, 1953) obstructs the surgical field. A small open mask is satisfactory and that shown in figure 4 is excellent. It was designed by the late Mr. A. Valentine and has been in use for many years. Deep anaesthesia is unnecessary and so contra-indicated, though the eye must be stationary for the examination. Valentine's curved forceps are often used to position the eye. A very clear airway must be maintained and this is easily done by the nurse who is steadying the head; she should extend the head at the atlanto-occipital joint and an artificial airway is rarely required.

Premedication. Atropine only is given unless the case is likely to return for repeated examinations, e.g. congenital cataract or suspected malignant disease. In these cases some sedation is given

as early as at six months and rectal thiopentone (1 gram for 50 lb (22.5 kg) body weight) is satisfactory.

For any delicate procedure, however brief (e.g. needling of a congenital cataract), an intratracheal tube is always used, as the surgeon should have perfect operative conditions. For intubation intramuscular suxamethonium chloride was tried, but was discontinued as the effect persisted longer than was wished. It is therefore given intravenously when used.

Most of these children are outpatients and can go home very soon after they leave the theatre. Any who have been given rectal thiopentone have usually recovered fully in two to three hours and are then allowed home.

The older children who come as outpatients are usually presented for incision and curettage of chalazion. Here satisfactory if not perfect results can be obtained with nitrous oxide oxygen and trichloroethylene administered through a standard dental nose piece; again the recovery time is very brief. A small dose of intravenous thiopentone is an advantage but, of course, delays recovery.

Operations for strabismus are very numerous. Sedative premedication is always given and frequently is quinalbarbitone sodium (0.6 grain per stone body weight—6 mg/kg approx.) one and a half hours before operation. Patients are then placed on a trolley and atropine 0.6 mg is given half an hour before operation. They are usually asleep on arrival at the theatre and anaesthesia is induced with nitrous oxide and oxygen with a little ether being added before the child is lifted from the trolley; this anaesthetic mixture is used throughout the operation. Intravenous thiopentone (less than 0.05 g. per year of age) and possibly a quick acting relaxant are then given slowly to allow a smooth induction and to facilitate intubation. The lungs are inflated to prevent straining at this stage, after which spontaneous respiration is allowed to return. The table is usually tilted. Postoperative vomiting in these cases would appear to be common. One is told that vomiting frequently occurs if analgesia alone is used, and I now think that some central effect follows the disturbance and pull on the extra-ocular muscles, causing the vomiting. I regret to say that I am resigned to an overall incidence of approximately 30 per cent but know that on some days every child is sick.

Adults. Premedication for intra-ocular operations is almost always atropine 0.8 mg and pethidine 100

FIG. 4
Showing Valentine's mask which allows full access to both eyes.

mg one hour before operation. This is because of the tendency for morphia and its closer derivatives to cause vomiting. Young adult males are treated differently, being given papaveretum 20 mg and scopolamine 0.45 mg one and half hours before operation. This is allowed because men of this age group seldom vomit following morphia and because the extra sedation helps to produce the desired pattern of anaesthesia and subsequent recovery. After only pethidine the reflexes may be somewhat brisk when one is trying to minimize the doses of intravenous and inhalational anaesthetics. Half this dose is also given occasionally to older subjects who are very large or alcoholics.

For intracapsular extractions, and in all cases where a reduced intra-ocular tension is desired, tubocurarine hydrochloride is given usually in the dose of 15 mg; this is occasionally increased to 20 mg for the robust and, on rare occasions, to 25 mg for very large adult males and for alcoholics. It is given as a single dose and is followed by thiopentone up to 500 mg which is given in divided doses to the bad risk cases. Inflation of the lungs with oxygen precedes spraying of the trachea and intubation with a No. 10 cuffed tube; to avoid possible straining the cuff is inflated only if there is considerable air leakage. Respiration is controlled throughout on a circle absorber using nitrous oxide 3 litres and oxygen 1½ to 2 litres with a minimal concentration of either chloroform or ether. The former is chosen for all cases except diabetics, because it is the smoothest of all inhalational anaesthetics and is, in my experience, less likely to cause vomiting than ether. It causes some loss of vasomotor tone and so will assist in reducing the blood pressure and intra-ocular tension; only two measured drams are put in the bottle of the Boyle's machine and usually one dram remains at the finish of the operation. Should the plane of anaesthesia become too light the chloroform vapour is strengthened rather than give additional intravenous drugs. Only rarely is it necessary to add more chloroform to the bottle and then it is always for a large patient and when the operation has continued for more than 30 minutes. At no time should the vapour concentration be suddenly increased as this produces cardiac arrhythmias. Weak ether vapour has always been given to diabetics and no harm has yet been observed to follow this practice. When the patient has been induced, and after a check has been made on the pulse and blood pressure, the head of the table is raised. If this alteration in position follows too rapidly on induction an undesirable fall in blood pressure can occur in the poor risk case.

With this technique a blood pressure of about 100 mm Hg is usual; no attempt is made to reduce it further and if this is the figure after the induction, the table will not be tilted at all. In some hypertensive patients the pressure remains high—even above 200 mm Hg; on these occasions the surgeon is asked if the tension is satisfactory and frequently it is so. This may be explained by reduction in the contents of the orbit from improved venous drainage and some reduction of filling from lowering of the blood pressure. If the tension is unsatisfactory the head up tilt is increased to about 15 degrees. By making the top end of the table horizontal the head can still be kept in a normal position for operating; this extra tilt has never failed to produce a satisfactory tension. Neostigmine (1 mg with atropine 0.6 mg) is given only if the tidal volume is unsatisfactory some minutes after the operation is finished. Statistics now being collected appear to show that when neostigmine is given vomiting will follow.

Extracapsular Extractions.

If a normal intra-ocular tension is required spontaneous respiration is retained; unconsciousness is induced with thiopentone and followed by a short acting relaxant. The trachea and cords are thoroughly sprayed with an analgesic solution, or 2 ml of lignocaine 4 per cent is injected through the cricothyroid membrane. It is desirable that slight coughing should follow the injection to spread the solution throughout the bronchial tree. The remainder of the thiopentone and a relaxant is then given. The lungs are inflated with oxygen prior to intubation with a No. 10 tube. Anaesthesia is maintained with nitrous oxide 6 litres and oxygen 2–3 litres and minimal ether or trichloroethylene; Bullough's (1952, 1955) circuit is often used. The table remains horizontal throughout the operation. With this technique the blood pressure does not fall, and any lowering of the intra-ocular tension is not appreciable. For extracapsular extractions a small

reduction of tension is sometimes requested with the proviso that the eye must not be too soft. On these occasions the technique as for intracapsular extractions has been used, but without table tilt; little blood pressure drop follows and the operative conditions have satisfied the surgeon.

These techniques have been described in detail as the principles involved cover the requirements for all ophthalmic operations in adults.

COMPLICATIONS

Postoperative Vomiting. In contrast to the cases of strabismus the vomiting rate following operations for cataract has been very low, below 5 per cent if neostigmine has not been given, but very much higher when it has. If vomiting occurs, the patient is given 50 mg of chlorpromazine intramuscularly immediately, and on the few occasions that it has been given vomiting has ceased quickly. This drug is not given pre-operatively, as the published results when this has been done do not suggest any improvement on our own, and we prefer to avoid the delayed recovery of consciousness which usually follows.

Ocular Complications. Causes of serious complications from the ophthalmological point of view are coughing, vomiting and restlessness, and they have occurred in this series, but they also occur, though less frequently, when analgesia alone is used. The fact remains that the surgeons are emphatic that these complications of general anaesthesia have caused little ocular damage provided that corneoscleral sutures have been used at the operation. No surgeon has published results showing the return of some useful vision in all cases and the figure of only 4 per cent of blind eyes is not always achieved (Stallard, 1946).

Deaths. In the hospital series no deaths have occurred in the first week from any cause. A case was lost in a nursing home and is of interest. The patient was a female, 75 years old and obese; a bad diabetic having 90 units of insulin daily; she had been in cardiac failure. She had already lost one eye following lens extraction elsewhere under local analgesia. The operation was very difficult and continued for 45 minutes. Increased tilt was requested during the operation. Under the conditions it was not possible to check the blood pressure frequently; shortly after completion of the operation there was sudden cardiac arrest. Ether and not chloroform was being used. I feel now that if a 15 degree tilt is to be used in such a patient, and it is doubtful if it should, blood pressure readings must be taken, if necessary by a third individual.

Surgically improved end results have been achieved from the use of general anaesthesia. Better results are obtained at operation and only occasionally is this advantage lost in the postoperative period. As far as the surgeons are concerned there is no dispute as to which is the better method, for let us not forget the patient has come to hospital to obtain improved vision.

THE FUTURE

Experience has led me to believe that the future trend of anaesthesia for ophthalmic surgery will follow that of general surgery, i.e. if the end results are better with anaesthesia than analgesia then the anaesthetists will be asked for assistance. The danger, as I see it, is that, particularly at holiday time, anaesthetists without special experience or training will undertake this work. One such informed me, with laughter, that a patient coughed hard as the lens was being withdrawn!

ACKNOWLEDGMENTS

I must record that to Mr. Nigel Cridland I owe a special debt of gratitude; he was the first to ask me to anaesthetize for cataract extractions and he pioneered the work. I am also indebted to Mr. Rex Parish for help in preparing this paper and on many other occasions.

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SOME OBSERVATIONS ON SEVERE TETANUS TREATED BY PARALYSIS AND I.P.P.R.

BY

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INTRODUCTION

During the five-month period from August 1 to December 31, 1955, twenty-five Nigerian patients with tetanus were admitted to the adult medical wards of Adeoyo Hospital, Ibadan. Seven of these patients who were suffering from tetanus of fatal severity were treated by muscular paralysis and intermittent positive pressure respiration (i.p.p.r.). By this means one was saved from an otherwise certain death. This case was reported in detail by Kirkpatrick et al. (1956). We present here some of the problems arising during the use of this technique because we consider that they are worthy of further investigation. To provide a foundation for these observations we first describe the criteria for selecting the seven patients for respirator therapy, and then give some details of the technique itself.

THE ASSESSMENT OF THE SEVERITY OF TETANUS

Tetanus is a disease which follows such a variable course that a correct assessment of its prognosis in each case is essential before the efficacy of any special treatment can be established. An unfavourable prognosis can be deduced from:

(*a*) A short period of onset as described by Cole (1951).

(*b*) An increase in the severity or frequency of spasms after the commencement of heavy sedation.

(*c*) An increase in the patient's temperature above 103°F (39.3°C).

Tables I, II and III show the relation between these prognostic factors and the mortality amongst eighteen patients admitted during the period under review who were treated by sedation only. It must be remembered that this is a group from which some of the severest cases have already been removed.

TABLE I

Mortality in relation to the period of onset.

	Period of onset in hours				
	Unknown	Under 25	25–49	49–73	Over 73
Died	3	4	1	0	0
Lived	0	0	3	2	5

TABLE II

Mortality in relation to increasing severity or frequency of spasms after start of sedation.

	Increase	No increase
Died	7	1
Lived	1	9

TABLE III

Mortality in relation to maximum body temperature during illness.

	Maximum temperature (Fahrenheit) during illness				
	Under 101°	101–102°	102–103°	103–104°	Over 104°
Died	0	0	1	3	4
Lived	3	4	2	1	0

*At present at the Poliomyelitis Unit, Infectious Diseases Hospital, Portsmouth.

THE SELECTION OF PATIENTS FOR RESPIRATOR THERAPY

The indications for commencing the respirator therapy in each of the seven cases for which it was used are shown in table IV.

No patient was treated by paralysis and i.p.p.r. unless we considered that a fatal outcome was both inevitable and near at hand if therapy were to be continued along conventional lines by heavy sedation only. Had the respirator treatment not been instituted when it was, each of these patients would definitely have died within a period of 24 hours.

TABLE IV
The indications for commencing the respirator treatment.

	Prognostic Factors			
Case No.	Period of onset in hours	Increasing spasms	Temperature (Fahrenheit) at start of respirator therapy	Other indications
1	21	Yes	99.0°	Failing circulation during spasms
2	6	Yes	100.0°	Sudden respiratory failure
3	72	Yes	104.8°	
4	48	Yes	104.2°	Aspiration pneumonia
5	Negligible	Yes	104.0°	Fulminating tetanus
6	48	Yes	104.4°	
7	4	Yes	103.8°	

THE TECHNIQUE OF PARALYSIS AND I.P.P.R.

Briefly, the general technique for the treatment of the respirator cases consisted of oral intubation under thiopentone and suxamethonium chloride, maintenance of a completely flaccid paralysis with laudexium methylsulphate (Laudolissen) given intravenously, and i.p.p.r. continued in six cases with a Radcliffe respirator (Russell and Schuster, 1953). The patient who recovered was ventilated with a Clevedon respirator (Macrae et al., 1954). We do not consider that the difference in design of the two types of respirator had any bearing on the outcome of these cases. Tracheotomy was performed within a period of 24 hours after the start of respirator treatment.

The patient's posture was changed from side to side and general nursing care given every 4 hours. Endotracheal suction was performed at least 4-hourly or more often if needed. The chest was examined several times daily and physiotherapy given as required. The water in the Radcliffe humidifier was kept at 49°C (120°F), and the aspirated mucus was never viscid. The respiration rate was fixed at either 13 or 16 a minute, and the inflating pressure between 18 and 25 cm of water. The minute volume was usually between 8 and 10 litres, being kept deliberately on the high side.

Control was by hourly rectal temperature, pulse, and blood pressure readings, the minute volume and inflating pressure being noted as required. On the last patient we also recorded the tidal volume hourly. A record was kept of the fluid intake, volume of urine output, and the urinary chloride excretion. The alkali reserve, serum chlorides and urine pH were estimated daily if possible. Other biochemical estimations and chest radiography were performed as and when the facilities were reasonably available. Unfortunately we were not able to obtain adequate electrocardiographic control.

All the patients received 50,000 international units of antitoxin intramuscularly on admission, 2,000,000 units of soluble penicillin daily, and other antibiotics as necessary. Sedation with sodium amylobarbitone was given if needed. A continuous intravenous drip was kept running, the relaxant being mixed with the fluid in the bottle. In some cases feeding with a high protein milk mixture was carried out through a stomach tube. The urine was drained 2-hourly through an indwelling catheter, and sulphamezathine was given routinely to control urinary infection.

PROGRESS AND OUTCOME OF THE RESPIRATOR CASES

The progress and complications of the seven cases treated by the respirator technique are summarized in table V. The patient who recovered had to be maintained in a paralysed state for 15 days before his muscle tone could be allowed to return without convulsions reappearing.

The major complications which occurred after the beginning of respirator therapy were:

(*a*) *Pulmonary atelectasis and infection.* This is the great hazard of respirator therapy, but only in case 6 did the infection become uncontrollable and definitely cause death.

(*b*) *Hypertension.* This was precipitated by carbon dioxide retention due to atelectasis. But it was observed many times to persist after the bronchial obstruction had been relieved and when the pulmonary aeration as judged by clinical auscultation and the measurement of minute ventilatory volume, was considered to be quite sufficient. Routine estimation of the alkali reserve and urine pH indicated that there was no chronic underventilation in any of these patients.

(*c*) *Vasomotor instability.* Hypertension was sometimes associated with a wildly fluctuating systolic and diastolic pressure. At times the pulse rate was also very variable.

(*d*) *Hyperpyrexia.* Five patients had a rectal temperature of 103.8°F or above when the respirator therapy was commenced and in four cases this was followed by a spontaneous fall in temperature to near normal figures within 12 hours. Subsequently three of these patients developed terminal hyperpyrexia of a different origin.

(*e*) *Renal failure.* Case 3 maintained an adequate output of urine, but its concentration fell progressively to a specific gravity of 1010. This was accompanied by severe azotaemia and also by marked sodium chloride retention. The other patients had azotaemia of varying degree.

DISCUSSION

The mortality associated with this series.

It is a certainty that by the use of the respirator technique life may be prolonged by several days in the severest forms of tetanus. Consequently, we

TABLE V

Progress and complications of the respirator cases.

Case No.	Time of death after start of i.p.p.r.	Immediate cause of death	Atelectasis	Persistent hypertension or vasomotor instability	Hyperpyrexia after start of i.p.p.r.	Maximum blood urea mg.%
1	Recovered		Yes	No	Maximum 102.8°F due to chest infection	59
2	6 hours	Accidental slipping of tracheotomy tube	No	No	No	—
3	5 days	Renal failure	No	No	Persisting 103–104°F for 4 days, then fall	190
4	5 days	Undetermined	Yes	Yes	Terminal 105.2°F	96
5	4 days	Undetermined	Yes	Yes	Terminal 107°F	50
6	8 days	Toxaemia from chest infection	Yes	Yes	Terminal 104.8°F	100
7	5 days	Undetermined	Yes	Yes	No	38

are of the firm opinion that a proportion of otherwise moribund patients can be saved in this manner. But this series is distinctive because the cases were all of extreme severity. Perhaps, had the patients selected for respirator treatment been those in whom the prognostic criteria were not quite so unfavourable, we might have saved more lives. There is a criticism that the delay in instituting the régime of full paralysis and i.p.p.r. until it was certain that the patients were about to succumb may have allowed irreparable damage to occur from anoxia which could have been avoided by an earlier change in the treatment. Also, had we, on starting this type of therapy, the experience and information, some of which we present here, the mortality in this series might have been lower.

Hyperpyrexia and circulatory complications.

In this small series of cases we have repeatedly encountered hyperpyrexia, hypertension, and vasomotor instability.

Hyperpyrexia is noted by Cole (1951) as a fatal and terminal event in tetanus. We can now distinguish at least four different types of pyrexia associated with this disease:

(*a*) Pyrexia caused by dehydration and which is reversed by intravenous fluid therapy.

(*b*) Pyrexia due to pulmonary atelectasis or infection.

(*c*) Hyperpyrexia accompanying severe muscular spasms and which is reversed by instituting the regime of total paralysis and i.p.p.r.

(*d*) Hyperpyrexia which occurs as a terminal event in an already paralysed and fully hydrated patient, and which is not explicable by the degree of pulmonary infection which may be present at the time of death.

Hypertension or vasomotor instability associated with adequate pulmonary ventilation during the use of this technique has been noted before, by Lassen et al. (1954) and by Forrester (1954). Our own experience is of prolonged periods of hypertension and of fluctuating blood pressure, precipitated by carbon dioxide retention due to a known atelectasis or bronchial obstruction, but frequently persisting after this local respiratory obstruction has been relieved. Obviously the adequacy of pulmonary gas exchange can be verified indisputably only by estimating the partial pressure of carbon dioxide and the oxygen saturation in the arterial blood. Hence facilities for precise and repeated arterial gas analysis are essential as a basis for further work on this problem.

Tetanus of the brain stem.

Lassen et al. (1954) have already pointed out that the technique of paralysis and i.p.p.r. may expose new manifestations in the symptomatology of severe tetanus. By both prolonging life and eliminating spasm and anoxia from the causes of death, this technique uncovers an entirely new field for clinical observation and investigation.

In experimental work with rabbits, Wright et al. (1950) have demonstrated specific autonomic and somatic manifestations of brain stem tetanus. By inoculating tetanus toxin into either the facial, vagus, or hypoglossal nerve the syndrome of bradycardia, strabismus, torticollis, immobility of the vibrissae, and salivation was produced. Bradycardia occurred only in short bouts, but these could be precipitated by stimulus. After injection of toxin into the vagus nerve, the pattern of onset of these symptoms was related to the anatomical propinquity of the vagal centre to each cranial nucleus subserving a discrete contribution to the syndrome. By radio-active tracer studies Wright et al. (1951) have further shown that in experimental rabbit tetanus the toxin can ascend from the sciatic nerve, through the spinal cord to the medulla. This in no way prejudices the view of Payling Wright (1955) that the toxin may also reach the motor nucleus of the fifth cranial nerve by direct diffusion from the blood stream at the area postrema in the floor of the fourth ventricle. In yet another investigation, Wright (1953) has related to the site of inoculation the differences in minimal dosage of toxin required to produce a fatal intoxication in rabbits. It was shown that the medulla is exquisitely sensitive to a direct injection of tetanus toxin. Medullary failure is stated by Knott and Cole (1952) to be a cause of death in tetanus. Baker (1942, 1943) in histological studies of the central nervous system in thirteen fatal cases in man, not only noted destructive foci in the midbrain, pons, and medulla, with a tendency to involvement of the tenth nerve nucleus,

but also correlated the severity and size of the lesions with the duration of the illness before death.

The characteristic clinical manifestations of tetanus intoxication of the spinal cord are frequently associated with comparatively little change in the histological appearance of the internuncial and anterior horn cells in the grey matter of the cord. It is, therefore, a reasonable supposition that the effect of the neurotoxin on the brain stem is far more widespread than the anatomical extent of the lesions which may be observed there microscopically. Excessive salivation, so frequently seen in severe tetanus, or in its "cephalic" form, is probably an active hypersecretion rather than a passive accumulation of mucus from dysphagia.

Our impression—at this stage it can be no more than conjecture—is that terminal hyperpyrexia, persistent hypertension, and vasomotor instability displayed by our own patients was due at least in some measure to involvement of the brain stem centres and central connections of the autonomic system in the tetanic process. It is not unlikely that this was the direct cause of death in three of the patients, namely cases 4, 5, and 7.

Clearly, the problem of adequately treating very severe tetanus is far more complex than one of simply respiring a paralysed patient until the muscular spasms have burnt themselves out. We are optimistic of further therapeutic advance along this line, but it may yet be shown that in some patients damage to the medullary centres by the toxin is so severe as to preclude the likelihood of survival, despite all forms of treatment.

Other effects of tetanus toxin.

It has been suggested that tetanus toxin may affect visceral tissues such as the myocardium (Lassen et al., 1954; Van Heyningen, 1954). Since severe tetanus is frequently accompanied by periods of anoxia, and by pulmonary infection, a secondary bacterial toxaemia with its own sequelae is often present. We have seen no direct evidence that in clinical tetanus the toxin acts in any way other than as a neurotoxin.

Nitrogen metabolism in tetanus.

We consider that azotaemia encountered in some of these patients was caused by a combination of impaired renal function together with excess urea production.

Impairment of renal function may be due to: (*a*) anoxia in the earlier stages of the illness; (*b*) toxaemia from secondary infection; (*c*) haemodynamic "back pressure" from the intermittent positive endobronchial pressure used for respiration.

Undoubtedly there are changes in the visceral blood flow associated with the technique of i.p.p.r. In relation to hepatic function, Astrup et al. (1954) have shown that a temporary lowering or even reversal of the plasma albumen/globulin ratio occurs with the institution of i.p.p.r. for patients with respiratory paralysis from poliomyelitis. This change was not observed in patients with severe paralysis but who were still able to breathe spontaneously.

An additional complication, regarding our patients, is found in the suggestion by Kenny (1954) that the renal excretion of urea is on a rather different basis in West Africans than it is in Europeans.

Excess urea formation is due to an increase in the breakdown of tissue protein. In tetanus there may be a marked "catabolic phase" comparable with that following surgical operation as described by Wilkinson et al. (1950). In this "catabolic phase" tissue protein is broken down faster than it can be synthesized, no matter how much dietary protein is supplied to the patient. Wilson and Care (1955) recorded a possible instance of negative nitrogen balance in a case of tetanus, even though the patient was receiving a high protein intake.

The problem is very relevant, since the administration of a high protein mixture through a stomach tube to a patient who has an increased catabolism can readily result in serious retention of nitrogenous material. This actually happened to case 3 of our series. It can be shown, using data quoted by Gamble (1954), taking into account the known protein intake, the urinary sodium chloride excretion, and the specific gravity of the urine, that in this patient the azotaemia might theoretically be attributed solely to renal failure. How much more, therefore, would it have been exacerbated by an excess of urea production from increased catabolism.

Careful nitrogen balance studies on patients with tetanus would be of value.

Electrolyte balance in tetanus.

Case 3 of our series had gross chloride retention. His urinary chloride output remained low despite a mistakenly heavy intake of sodium chloride. Allott (1957) has recently discussed the association of electrolyte retention with various forms of intracranial lesion including bulbar poliomyelitis. Presumably the suppression of chloride excretion in our patient was but another manifestation of this phenomenon. As far as we know, it has not been described before as occurring in tetanus. This suppression of chloride excretion may be due to a mechanism similar to the one postulated by LeQuesne (1954) in relation to electrolyte retention after surgical operation—namely, changes in the secretion of adrenocorticotropic hormone, superimposed upon a renal haemodynamic factor. Its immediate practical importance is the demonstration of the danger inherent in the exclusive use of the Fantus test for urinary chlorides for the purpose of regulating the sodium chloride intake without regard to the serum electolyte levels.

SUMMARY

Seven selected patients with tetanus of fatal severity were treated by means of paralysis and i.p.p.r. The method of selection, the technique of treatment, and the final outcome are described. The causation of the symptoms encountered is discussed. There is strong evidence that in severe forms of tetanus the toxin acts on the brain stem centres. Hitherto the clinical manifestations of this action have been either largely masked by the presence of muscular spasms or forestalled by the early death of the patients. The therapeutic technique of total paralysis and i.p.p.r. provides an opportunity for the isolation and critical examination of these manifestations. Further investigation into nitrogen and electrolyte balance in tetanus is also advocated.

ACKNOWLEDGMENTS

We wish to express our appreciation to Professor A. Brown and Dr. J. R. Lauckner for giving us free access to their patients, and for their advice and encouragement. We gratefully acknowledge our debt to Dr. C. R. Kirkpatrick for his supervision of the first case. Our thanks are also due to Dr. P. Doherty for help in the care of the patients; to Sister Pratt and her nurses for coping magnificently with an unfamiliar and exacting form of therapy; to our surgical colleagues for performing the tracheotomies; and to Dr. Edozien for the biochemical investigations.

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A VAPORIZER FOR FLUOTHANE

BY

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FLUOTHANE — bromochlorotrifluoroethane — is a powerful volatile anaesthetic agent developed and produced by Imperial Chemical Industries. It is so potent—less than 2 per cent of Fluothane vapour sufficing for anaesthesia in the great majority of subjects—that it is essential that one should have fine accurate control of the mixture administered and be able to raise or reduce its strength by small fractional percentages.

At the beginning of our clinical trials of Fluothane, the drug was given via the Trilene (trichloroethylene) bottle on a Boyle's machine, nitrous oxide and oxygen being used as the vehicle. This method gave varied and not altogether satisfactory results.

According to Mapleson (1957) there are no less than ten factors which can affect the percentage of trichloroethylene delivered to a patient by a Boyle's bottle. In an attempt to understand our rather uneven clinical results, the effects of some of these factors on the strength of Fluothane obtained from a similar bottle were investigated in the laboratory.

Method. Compressed air was led via an accurate rotameter to a Boyle's bottle containing Fluothane. The bottle was surrounded by a water bath kept at 19°C. The resulting vapour was passed through a mixing chamber—to avoid inaccuracies from channelling—and was then sucked by a small Edwards pump through a Raleigh gas interference refractometer. Some scores of readings were taken under a wide variety of conditions. It was found that the position of the plunger, the rate of air flow, the amount of Fluothane in the bottle, and, if the water bath was not used, the passage of time (Falkner Hill, 1957), all had a very marked effect on the strength of Fluothane vapour produced. If the control lever was fully opened, whatever the rate of flow and whatever the amount in the bottle, depression of the plunger to just above the surface of the liquid produced some 9 per cent of Fluothane vapour—a dangerously high concentration.

A position of the control lever was found such that with the plunger at the top of its travel and with 3 oz (1 oz = 28.4 ml) of Fluothane in the bottle a 4 litre flow produced a 1.85 per cent vapour, that is, a useful clinical strength. The lever was then fixed in this position, the plunger kept at the top, and observations were made of the effect of varying the rates of flow and the amount of liquid in the bottle. Some of these readings are shown on the graph (fig. 1). It will be seen that increasing or reducing the flow correspondingly increased or reduced the strength of Fluothane—a 2 litre flow producing only 0.75

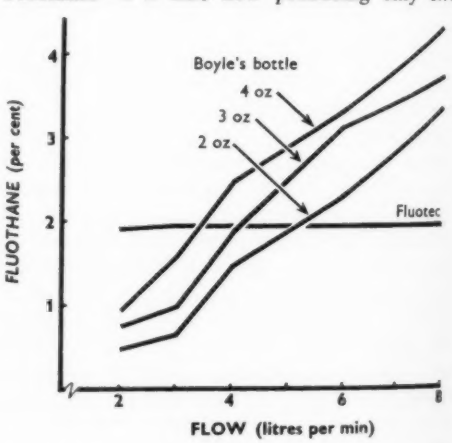

FIG. 1

Graph showing the effect of varying the flow rates and the amount of the liquid in a Boyle's bottle on the strength of Fluothane vapour produced, contrasted with that delivered by a Fluotec inhaler containing anything from 50 to 150 ml and with the dial turned to 2 per cent.

per cent, while an 8 litre flow raised this figure to 3.82 per cent. The amount in the bottle caused similar but less wide variations—a flow which produced 1.4 per cent with 2 oz in the bottle produced 2.5 per cent when the content was increased to 4 oz.

It was felt that these extremely wide variations resulting from alterations in gas flows and the amount of liquid in the Boyle's bottle explained many of our clinical results and were of such an order as to make this apparatus as at present designed unsatisfactory if not unsafe for the administration of Fluothane.

The accuracy of a prototype Fluotec vaporizer was then similarly tested with a refractometer. With any flow rate from 4 to 10 litres the Fluotec was found to be accurate throughout its range to within 0.05 per cent. This accuracy was affected neither by the amount of liquid in the vaporizer —providing that any at all could be seen through the observation window—nor by the passage of time. The built-in thermostat worked so accurately that the same values to within 0.01 per cent were recorded when the inhaler had been in constant use for over an hour. With flow rates below 4 litres a little inaccuracy was detected at the extremes of the range, but in the middle ranges, e.g. 2 per cent, the accuracy as shown on the graph was impeccable even with only a 2 litre flow.

For the last six months we have been carrying out clinical trials with Fluotec vaporizers, at first with a prototype and later with the improved production models. These inhalers have been used by nearly twenty different anaesthetists attached to this department on many hundreds of patients anaesthetized for a wide range of surgical procedures. Sturdily and beautifully made, they have proved extremely satisfactory in use, and have elicited nothing but praise. They can be warmly recommended.

ACKNOWLEDGMENTS

I would like to express my thanks to Messrs. Cyprane Ltd. for the loan of the prototype Fluotec vaporizer and Imperial Chemical Industries Ltd. for supplies of Fluothane.

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BOOK REVIEW *continued from page 318*

thetist, and ward sister. The question of the right age to operate on these babies may be a matter of opinion, but the criteria of optimum condition of the baby as described in this book, which are largely those adopted by Kilner and Hunter, are among the most important lessons that have been learned in the handling of these infants. The fulfilment of these conditions may demand a considerable stay in hospital before operation is undertaken, and such a reasonable attitude rarely appeals to the administrators of a busy general hospital. The nursing care of these infants makes heavy demands upon the nursing staff, which is probably only possible in the special units. The endotracheal technique and management of the anaesthetic, as described in the book, follow the lines developed by Magill, Gillespie and Hunter.

It is difficult to quarrel with the anaesthetic aspects that are mentioned, and Holdsworth's use of local infiltration to do a primary repair of the lip in the first few days of life seems a reasonable procedure. Though general anaesthesia is perfectly feasible for these early repairs, probably local anaesthesia is less wearing for the surgeon. After ten days of age the child becomes restless under a local, and it is probably then wiser to wait and do it under general anaesthesia a month or two later.

The book should certainly be read by all who are faced with anaesthetizing babies for hare lip and cleft palate.

P. A. Shackleton.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

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(*Continued from page* 240)

The small number of deaths between fifteen and twenty-five may be partly due to the circumstance that surgical operations are but seldom required at this period of life; but the decrease after the age of forty-five cannot be explained in this way; for persons become more liable to require surgical operations as they advance in years. Operations are often performed in infancy and old age, periods at which deaths from chloroform have not been recorded. The greatest proportion of deaths having occurred from thirty-five to forty-five, when the system is often more robust than at any other period, it cannot be supposed that an inability to bear the usual dose of chloroform, when carefully administered, is the ordinary cause of death from this agent.

Idiosyncrasy. The accidents from chloroform have frequently been attributed to idiosyncrasy in the patient. This, it may be observed, is not to give an explanation of them, but merely to state that they depend on something we do not understand; that something, however, being in the person to whom the accident happens. This view receives apparent support from the supposition that the chloroform has been inhaled in exactly the same manner in the fatal cases as in other instances; but this apparent support fails when it is pointed out that the supposed same manner is only an equally uncertain manner. The different effects that have been produced on the same patient at different times, and the great number of instances in which medical men have failed to make the patient insensible, show that most of the usual modes of exhibiting chloroform are extremely uncertain.

What most completely meets the question of idiosyncrasy, however, is the circumstance that in no fewer than eleven out of the fifty recorded cases of death from chloroform, the patient had previously inhaled this medicine without ill effects. In two other cases also, previous attempts had been made to make the patient insensible without success, on the day on which the accident occurred. In the above table of fatal cases, those are indicated in which previous inhalations had taken place. In twenty-nine cases, I have concluded that the patient had not previously inhaled, for the medical man, having given an account of the state of his patient, and his reasons for administering the chloroform, would certainly have mentioned such a material fact as a previous inhalation if it had occurred. There are ten cases of which only a meagre account is given, and where a previous administration of chloroform may possibly have taken place without being mentioned; but if only eleven, out of the fifty patients, who died from chloroform, had inhaled it

previously without ill effects, it is very clear that the fact of having inhaled it with a favourable result, gives no immunity from the possibility of accident. It would be impossible to say what proportion of the patients who have inhaled chloroform have inhaled it more than once, but it is not probable that they amount to more than 22 per cent., if so many.

Alleged Impurity of the Chloroform. At one time accidents from chloroform were loosely attributed to impurity in the medicine, but this was only a guess, and is opposed to the facts. No case of accident has been traced to this cause, and in nearly all the cases of which the details are given, it is distinctly recorded, either that the chloroform was examined and found to be of good quality, or else that chloroform out of the same bottle had been used in other cases without ill effects. I have not thought it necessary to state this in quoting the individual cases.

Apparatus employed. Accidents were at one time, and in one quarter, attributed to the use of inhalers; and it is curious that this allegation was made at a time when no death from chloroform had yet occurred in any cases in which an inhaler was used, except one in America, and one in France, the accounts of which had not reached this country. It is possible that death might be occasioned by want of air from the use of a faulty inhaler, and a case will be mentioned in which this apparently occurred in the administration of sulphuric ether, but there is no recorded case of accident from chloroform in which death was occasioned in this way. In the cases of death previously recorded, a handkerchief, a piece of folded lint, hollow sponge, or some such simple contrivance, was used in thirty-four instances; in twelve cases, an inhaler of some kind or other was used; and in four cases, it is uncertain what were the means employed.

Alleged Exclusion of Air. The assertion has often been made that death might be caused by the vapour of chloroform excluding the air, and so causing asphyxia; but it has already been pointed out in this work that the physical properties of chloroform do not allow it to yield a quantity of vapour which would have that effect, and in much smaller quantity than this the vapour kills by a quicker way than asphyxia, I believe that the only elastic fluids which can cause death simply by excluding the atmospheric air are nitrogen and hydrogen.

Alleged Closure of the Glottis. At the trial which took place in Paris respecting the death of a porcelain dealer previously mentioned, M. Devergie gave evidence, and after saying that chloroform might cause death as a poison, if given in undue proportion, he added: "Also it closes the glottis, and offers an obstacle to respiration. Employed by M. Demarquay on himself, in very small doses, closure of the glottis was occasioned. It was possible that Le Sieur Breton had experienced that accident, and in that case the most able surgeon could not prevent death."

I have not met with M. Demarquay's account of his experiment, but I am happy to know that he did not die of the closure of the glottis. It may fairly be denied that a person could commit suicide in this manner if he wished, for he would either have to give up the attempt, or receive the vapour into his lungs, and experience its

specific effects. When animals are placed in mixtures of vapour and air, they always breathe them, whatever the strength; and if the vapour amounts to eight or ten per cent., they die much more quickly than they would of mere closure of the glottis. Vapour of chloroform, when not largely diluted with air, is apt to cause cough and closure of the glottis, as soon as a little of it reaches the lungs; but this, so far from being a source of danger, is, as a general rule, a safeguard, by its preventing the patient from readily breathing air which is highly charged with vapour.

In commenting on the fatal case No. 12, which occurred in St. Thomas's Hospital, I have suggested that the accident might have happened from liquid chloroform being dropped into the throat; but liquid chloroform is very different from the vapour; it causes a lasting irritation if applied to a mucous membrane; when used for toothache, it often blisters the gums. The irritation caused by the vapour, on the contrary, is only momentary, and its local action ceases directly it ceases to be inhaled; for what is left in the air passages is immediately absorbed or expelled with the expired air. The glottis is not a vital organ of itself. Its closure only causes death by preventing the access of air to the lungs. The glottis does not remain permanently closed, I believe, from the contact of any elastic fluid, however irritating;* but it does from the contact of a liquid, and persons who die by drowning, die with the glottis closed, for they do not fill their lungs with water. Therefore, if the vapour of chloroform did cause persistent closure of the glottis, and if a person were to hold it by force to the patient, the death it would occasion would be precisely like that in drowning. Death by asphyxia is a comparatively slow one. I find that when the access of air to the lungs is entirely cut off, death does not take place in less than three minutes and a half in guinea pigs, and four minutes in cats. In dogs, the process of asphyxia is still slower. Mr. Erichsen states, that on taking the average of nearly twenty experiments, the contractions of the ventricles continued for nine minutes and a quarter after the trachea had been closed, and that the pulsations of the femoral artery also were perceptible for an average period of seven minutes and a half. The process of drowning in the human subject is well known to occupy some minutes; and even if the pungency of the vapour of chloroform should entirely prevent the patient from breathing, and the medical man could overlook the fact that breathing was not going on, it cannot be supposed that he would use the force, and have the perseverance to cause his patient to die slowly by asphyxia. If any patient, therefore, has died from closure of the glottis, it must have been one in whom there was a great tendency to sudden death from any slight interruption to respiration. I do not know the particulars of the case respecting which M. Devergie was giving his evidence, but in those fatal cases previously related, in which the symptoms are sufficiently described, it is not probable that death took place in any instance from closure of the glottis. In the sudden death

* Hydrochloric acid gas and ammonia are no exceptions to this rule, for they cease to exist as gases so soon as they come in contact with the moist lining membrane of the air passages. Carbonic acid gas will be treated of in another part of this work.

at St. George's Hospital (page 95), it is possible that the slight pungency of the vapour might assist the fear under which the patient was labouring in impeding the breathing, and thus add to the distension of the right cavities of the heart, under which the patient apparently died.

In 1855, two years after M. Devergie had given the above opinion, Dr. Black, of St. Bartholomew's Hospital, who has had great experience in the administration of chloroform, advanced a similar theory in the pamphlet previously alluded to. He did not, however, confine the effects of the supposed closure of the glottis to possibly causing a death here and there, as M. Devergie had done, but he attributed all the accidents which had happened to this cause, and not to the effects of chloroform in the system. He says that " the chloroform has not been even inhaled: its pungency was felt at the glottis, and its inspiration was immediately arrested. The patient would have removed the apparatus, but in this he was restrained. The struggle forthwith commenced, but up to the moment of his death, not a single inspiration took place." These remarks were not applied to a single case, but generally to the accidents from chloroform. Dr. Black says: " Any concentration of the vapour of chloroform which can be breathed is safe; any condition of dilution which forces the patient to cough or hold his breath is dangerous, and if persevered in for even half a minute, may be fatal. . . . We have only to attend to the breathing; we may disregard all considerations affecting the relative proportion of the chloroform in the air which is breathed; . . . if the patient breathes easily he is in safety, whatever be the amount of chloroform which is passing into the lungs."

In Experiment 28, previously related, where the respiration was kept up by a tube in the trachea, there could be no error in respect to the vapour of chloroform entering the lungs, when a bladder of air charged with ten per cent. of the vapour was substituted for the bladder of simple air; and the immediate paralysis of the heart was evident. An examination of the fatal cases, of which the particulars have been recorded, shows that death did not occur in the manner Dr. Black suggests. In the majority of the cases, the patients were rendered quite insensible by the chloroform, and the operation had either been commenced, or was on the point of commencing, when the fatal symptoms set in. In several other cases, the patients were partially under the influence of the vapour before the symptoms of danger commenced; and in the six cases where death occurred at the beginning of the inhalation, without loss of consciousness having been induced, the patients were not restrained in any way, and it was observed that they did breathe the chloroform; three of them were speaking up to the moment when the pulse stopped, and one took a full inspiration the moment before the fatal symptoms set in. It is only in eighteen of the fatal cases that there is any reason to suppose that the patient required to be held, and then only from mental excitement or muscular spasm, arising from the physiological effects of the absorbed chloroform. It is hardly possible that the struggles of a conscious patient from inability to breathe, would be mis-

taken for excitement or spasm caused by chloroform.

In a case, No. 34, which occurred at St. Bartholomew's Hospital whilst Dr. Black was present, and long before his pamphlet was written, the patient inhaled for five minutes and sank off into a state of complete insensibility without alarming symptoms. The inhalation was discontinued, the patient moved into a proper position, and the operation just about to be commenced, when Dr. Black found the pulse to become extremely feeble and fluttering. Surely this patient breathed the chloroform, and died without any spasm of the glottis. In Case 48, so minutely related by Mr. Paget, the boy made one long inspiration, and became suddenly insensible. In a few seconds, the pulse suddenly failed, and then ceased to be perceptible, but the breathing continued for at least a minute afterwards. There was certainly no closure of the glottis in this instance.

Alleged Exhaustion from Struggling. In cases where the patients have struggled violently whilst getting under the influence of chloroform, the accidents have been attributed to a supposed exhaustion caused by the struggling.* This opinion is, however, contrary to experience; for the patients who struggle violently are precisely those who bear chloroform the best, provided they do not breathe it in an insufficient state of dilution. They are generally cheerful and exhilarated by it, and are less liable to be depressed by its prolonged use, than those who come quietly under its influence. Although the patients who struggle bear the chloroform well, when it is carefully and judiciously administered, it is not improbable that the struggling has been now and then an indirect cause of accident. The muscular spasm and rigidity do not occur till about three-quarters as much chloroform has been absorbed as can be present in the system with safety; and, as the patients often hold their breath whilst struggling, and take deep inspirations suddenly and at long intervals, the greatest care is required that the vapour be administered in a very diluted state. In Cases 9, 44, and 47, the fatal symptoms came on whilst the patients were struggling; and in some other cases, the sudden failure of pulse occurred just after the struggling had ceased, rendering it probable that the patient inhaled too much of the vapour whilst struggling, or just as the spasmodic condition of the muscles was subsiding.

The circumstances just mentioned, are probably the cause why so many of the fatal cases occurred at that period of life when the body is most robust. Very nearly two-thirds (twenty-seven out of forty-one) of those cases in which the ages are recorded, occurred in persons of twenty years and under forty-five years of age, although the proportion of persons living at this period of life, in England and Wales, is only a little more than one-third of the entire population. The majority of the accidents from chloroform occurred also in the stronger sex, in which muscular rigidity and spasm are most frequent:—twenty-nine of the fatal cases happened to males, and only twenty-one to females. According to my experience, the females who inhale chloroform for surgical operations are nearly twice as numerous as the

* See Med. Times and Gaz., 1853, vol. ii. p. 562.

males; and although this may not be the proportion in every one's practice, it is probable that females inhale this agent quite as frequently as the other sex, in every part of the world.

Sitting Posture. In some of the early cases of death from chloroform, the patients were inhaling it in the sitting posture, and it was surmised that this circumstance was the cause of death. An examination of the account of the fatal cases, however, does not bear out this supposition. In thirty-one instances the patients were lying, in nine instances sitting, and there are ten cases in which the position is not mentioned, and where from the nature of the operation it may have been either one or the other. In fully one-fourth of the cases of which I have kept notes of the administration of chloroform, the patients were seated in an easy chair; and as in forty fatal cases in which the position is known, only nine, or less than one-fourth, were seated, it does not appear that the position of the patient has had any share either in causing or preventing accidents.

Supposed Effect of the Surgeon's Knife on the Pulse. Mr. Bickersteth alluded to a peculiar circumstance,* which he thought would account for several of the deaths attributed to chloroform. He relates three instances in which the pulse suddenly ceased on the first incision by the surgeon, and commenced again in a few seconds, the breathing going on naturally all the time. All the three cases were amputation of the thigh, and occurred in the latter part of 1851. Mr. Bickersteth did not observe the circumstance again during the two following years, and I have never observed it, although I have very often examined the pulse at the moment when the operation began, especially after reading Mr. Bickersteth's remarks. He supposes that the action of the heart was arrested by the shock of the incision, notwithstanding the patient was insensible. I should attribute the temporary stoppage of the pulse in these instances to the direct influence of the chloroform on the heart. The moment when the operation is commenced, is usually a few seconds after the inhalation has been discontinued, and when the effect of the chloroform is at its height. A portion of that which was left in the lungs having been absorbed, in addition to that which was previously in the system. And if the vapour inhaled just at last was not sufficiently diluted, it might paralyse the heart, but not so completely as to prevent the natural respiration from restoring its action, in those cases where respiration continues. I found in experiments on animals that, when the action of the heart has been suspended by the effect of chloroform, it can very often be restored by artificial respiration instantly applied; and it is extremely probable that an accident of this kind not unfrequently occurs during the administration of chloroform, and is remedied by the breathing, without being noticed. The pulse recovered itself, in the cases mentioned by Mr. Bickersteth, just as it does in animals after the heart has been nearly overpowered by chloroform.

* Edin. Monthly Jour., 1853, vol. xvii, p. 220.

(*To be continued*)

BOOK REVIEW

Pulmonary Complications of Abdominal Surgery. By Anthony R. Anscombe, M.S., F.R.C.S., Senior Lecturer in Surgery, St. George's Hospital, London. Published by Lloyd-Luke (Medical Books) Ltd., London, 1957. Pp. 121, Price 20*s*.

Postoperative chest complications have been a bone of contention between surgeons and anaesthetists for as many years as patients have separated these gentlemen. On the one hand these complications have been repeatedly laid at the door of the anaesthetist, with the strongest implication that one sort of anaesthetic is immune from them while another is followed by a high incidence. On the other hand, these suggestions, on carefully gathered evidence, have been repudiated not only by anaesthetists but by other serious observers throughout the world. Of the latter, one of the most noteworthy in this country is Brock whose now classic paper in *Guy's Hospital Reports* in 1936 first emphasized that the liability of a patient to develop a postoperative chest is more closely connected with such factors as the site of the operation than with which particular drug was chosen as the anaesthetic. So far as abdominal surgery is concerned, the old contentions will now surely be considerably weakened, if not resolved, by this scholarly monograph by Anscombe—an amalgam of his 1955 Moynihan Prize Essay, and his M.S. thesis on a similar subject. All the possible causal factors underlying postoperative " chests " are discussed, particularly from a physiological and mechanical point of view. It becomes clear that the anaesthetic, while not to be ignored, is far from being a major factor, if it is an important one at all. The anaesthetist will find excellent descriptions of the various clinical conditions which go under the general name of " chest ", as well as a very practical account of modern views of the mechanism of and the investigation of certain pulmonary functions. The 36 illustrations are all clear and helpful, and a very extensive list of references is appended. Anscombe's book is probably the most important up-to-date account of these troublesome complications, and it deserves the closest study from every surgeon and anaesthetist.

W. W. Mushin.

WORLD CONGRESS OF ANAESTHESIOLOGISTS—TORONTO 1960

The next World Congress of Anaesthesiologists is being arranged to take place in Toronto in 1960, from September 4 to September 10. All enquiries should be addressed to Dr. R. A. Gordon, Chairman of the Organizing Committee, 516 Medical Arts Building, Toronto 5, Ontario, Canada.

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CONTENTS

PAGE

EDITORIAL 293

ORIGINAL

Release of Adrenergic Catechols after the Adminstration of Hexamethonium Bromide 294

By L. W. Hall, M.A., B.Sc.(Vet. Sci.), Ph.D., M.R.C.V.S., Department of Veterinary Studies, University of Cambridge.

Experimental Studies with Prestonal. A New Short Acting Muscle Relaxant 303

By L. Rendell-Baker, M.D., B.S., F.F.A.R.C.S., Francis Foldes, M.D., H. Birch, M.B., Ch.B., D.A., and P. B. D'Souza, M.B., B.S., D.A., Department of Anesthesiology, Mercy Hospital, and Section of Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A.

Hypothermia for Cardiovascular Surgery: Acidosis in the Rewarming Period 310

By H. Barrie Fairley, M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, W. G. Waddell, M.D., C.M., National Research Council Surgical Research Fellow, and W. G. Bigelow, M.D., F.R.C.S.(C), Department of Surgery, University of Toronto, Canada.

PAGE

CLINICAL

General Anaesthesia in Ophthalmic Surgery 319

By H. B. C. Sandiford, F.F.A.R.C.S., Portsmouth Group of Hospitals, Portsmouth.

Some Observations on Severe Tetanus Treated by Paralysis and I.P.P.R. ... 326

By M. W. Glossop, M.A., B.M., B.Ch., D.A., The Poliomyelitis Unit, Infectious Diseases Hospital, Portsmouth, and M. D. W. Low, M.B., M.R.C.P., D.Obst.R.C.O.G., Department of Medicine, University College, Ibadan, Nigeria.

GENERAL INTEREST

A Vaporizer for Fluothane 332

H. J. Brennan, M.D., F.F.A.R.C.S., D.A., Department of Anaesthetics, The Royal Infirmary, Manchester.

On Chloroform and Other Anaesthetics: Their Action and Administration ... 334

By John Snow.

BOOK REVIEWS 318, 340

WORLD CONGRESS OF ANAESTHESIOLOGISTS 340

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PAGE

halmic
... 319
R.C.S.,
Ports-

etanus
.R. ... 326
B.Ch.,
fectious
and
R.C.P.,
Medi-
Nigeria.

... 332
, D.A.,
Royal

etics:
on ... 334

318, 340

... 340

NGLAND